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Introduction

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Neurotrophic factors – proteins promoting neuronal development and survival – have been known now for almost 50 years. Several aspects of their biology and mode of action are very well known, but many of their important features are still unexplained or even not studied. The articles in this multi-author review, therefore, mainly focus on the less-studied or controversial aspects of the structure and function of neurotrophic factors.

The name 'neurotrophic factor' is historical. Classically, three protein families are called 'neurotrophic factors': neurotrophins, the glial cell line-derived neurotrophic factor GDNF family and neuropoietins [(or ciliary neurotrophic factor (CNTF) family], since the first member of each family was discovered by its ability to promote neuronal survival. However, all neurotrophic factors also regulate important processes in the non-neuronal cells that are essential for the development and function of the organism. Less-studied non-neuronal functions of neurotrophic factors are reviewed by H. Sariola. Only recently, some studies have demonstrated that in addition to its crucial role in development and maintenance of the nervous system, GDNF appears to be critical for kidney morphogenesis and spermatogonial renewal. The multiple functions of neurotrophic factors in different tissues provide an interesting example of how an organism uses the same biologically active factors for several purposes. Many other growth factors, mainly known for their non-neuronal activities (e. g. some fibroblast growth factors, and insulin-like growth factors) have some trophic effects on selected neuronal populations, but are not called neurotrophic factors. This multi-author review deals mostly with the three 'historical' neurotrophic factor families.

Several neurotrophic factors influence neuronal populations that are affected in neurodegenerative diseases. GDNF, CNTF and neurotrophins have, in animal models, proven to be very promising drugs for the potential treatment of Parkinson's disease, Alzheimer's disease and several motoneuronal disorders. For these reasons, there has been great interest in unraveling the three-dimensional structure of these factors and their cognate receptors. Recent years have seen remarkable progress in the structural analysis of neurotrophic factors and their receptors, providing firm ground for rational drug design for neurodegenerative diseases. These aspects together with an evolutionary comparison of neurotrophic factors and their receptors are reviewed by M. J. Butte.

The diversity of neurotrophic factors and their receptors is increased by alternative splicing of their gene transcripts. Splice variants of neurotrophic factors and their receptors should have different functional properties. However, very little is known about the structural and biological differences of the splice isoforms of neurotrophic factors. This neglected topic will certainly become more important in the future and together with characteristic features of neurotrophin gene regulation is covered in the review by M. Metsis.

The receptor systems of all three classes of neurotrophic factors consist of different subunits. A few years ago, the p75 receptor for neurotrophins, as well as the GFRα1 receptor for GDNF, were considered to be only ligand-binding components, delivering the ligands to the signalling receptor tyrosine kinases. Recent ample evidence suggests that both receptors, although also functioning as co-receptors, can mediate signals to cells independently of their receptor tyrosine kinases. Despite serious efforts, our knowledge about the mechanisms of receptor-co-receptor interactions and the implications of these interactions for intracellular signalling are still very limited. For example, the earlier view that TrkA is a high-affinity receptor and $p75^{NTR}$ is a low-affinity receptor seems to be changing. According to the currently favoured model, both receptors are needed to create a high-affinity binding site. These fascinating matters are discussed by K. E. Neet and R. B. Campenot.

These authors also discuss another largely neglected area in neurotrophic factor research – cell biology. That cell biological studies of neurotrophic factors are still in their

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embryonic stage is exemplified by the fact that even the sub-cellular localization of Trk and p75 receptors on the plasma membrane is still poorly documented. On the other hand, the importance of these types of study is becoming increasingly evident. For example, the GDNF receptors, Ret and GFRα1, are differently organized in the plasma membrane: GFRα1 is located inside, but Ret outside the membrane lipid rafts. Moreover, GDNF is able to recruit Ret to the rafts, that is changing the nature of intracellular signalling. In addition, how the neurotrophic factors that bind the receptors at synaptic terminals affect biochemical and transcriptional responses at the neuronal soma are poorly understood. Furthermore the biological meaning of retrograde transport of the neurotrophic factors is also not clear. Neet and Campenot also shed light on these interesting processes.

The most important functional attribute for the neurotrophic factors is their ability to actively promote neuronal survival. In a classic target-derived trophic factor model, a developing organism uses the capacity of neurotrophic factors to regulate the proper number of neurons during a specific developmental period, in many cases corresponding to the stage when the target is being innervated. The best-characterized example – how neurotrophins regulate the number of peripheral sensory neurons – is discussed in detail by P. Ernfors. The trophic factors regulating the number of central neurons is, however, less well understood. Recently, another developmental period of neuronal death has been identified, during which the number of neurons is regulated by neurotrophic factors, as decribed here by Ernfors, and also by F. D. Miller and D. R. Kaplan. The molecular pathways regulating apoptosis during this novel period are connected to cessation of the mitotic properties of neuroblasts, and are regulated by neurotrophin-3.

The intracellular mechanisms of the anti-apoptotic activity of NGF have only recently begun to be understood. Whether other neurotrophic factors use similar pathways is almost unstudied. Recently, in a fashion similar to that seen in the immune system, neuronal apoptosis has been found to be regulated by two different pathways: survival is promoted by trophic factors (neurotrophins) and active killing is executed by the death receptor ($p75^{NTR}$). These conceptually novel findings are described in the article by Miller and Kaplan.

In addition to trophic activities, neurotrophic factors also stimulate neurite outgrowth. Numerous investigations have examined how neurotrophins regulate neurite growth and branching, pathfinding, synaptogenesis and synaptic plasticity. These aspects are reviewed by A. K. McAllister. Despite these extensive studies, however, the biological role of neurotrophic factors in neuritogenesis, especially in the central nervous system, is far from understood. Many roles have been established in vitro, either in cultured neurons or brain slices, but not always confirmed in vivo. Presumably the establishment of neuritic connectivity and synaptic plasticity are complex processes involving many other molecules, and neurotrophic factors are just one part of the complete molecular machinery.