

Neurotrophins

Molecular links between the immune and nervous systems

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ABSTRACT

The rapid evolution of molecular biology over the past few decades has revolutionised our knowledge in pathophysiology and pharmacotherapeutics of many diseases including the immune and nervous systems. The growth factors, neurotrophins, happened to be orchestra conductors for many biological systems and their potential use especially for therapeutic purposes cannot be overlooked.

Keywords: Neurotrophin growth factors, neurotrophin receptors, cell signalling, immunocytes, neurocytes, allergic diseases, rheumatic diseases and infectious diseases.

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Neurotrophins are glycoproteins isolated for the first time, in the early fifties, from brain and peripheral nerves.^{1,2} They were later found to have wider tissue distribution and exert biological effects on a wider number of biological systems other than the nervous system.³⁻¹⁰ They were also found to be involved in different pathological processes such as autoimmune pathology, allergy and defence against infection.^{3,5-12,15-18} Thanks to progress in molecular biology over the past few decades which made it possible to investigate these molecules in more depth. In this review, discussion will be focussed upon physiological and pathological roles which these molecules play with emphasis on immune mediated disorders.

Physiology. Neurotrophins are target derived soluble growth factors, essential for regulating survival, development and differentiation of the central and peripheral nervous system in mammals.¹¹ Extra-neuronal effects of these molecules are increasingly being described in many systems throughout development such as endocrine, reproductive, hematopoietic and immune systems.^{7,11-12,14,16,19,20}

These neuropeptides which include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and neurotrophin-3, act via binding to high affinity tyrosine kinase (trKA) the lower affinity p75 neurotrophin receptors (trKB) and trKC. Binding to these receptors occur independently from each other.²² Different signalling events result from such binding, which promote cell survival and differentiation and paradoxically cell death in certain setups. The trophic and cell death properties of neurotrophins are dependent upon the relative ratio of receptors and the persistent nature of signalling events.²² Functionally antagonistic actions on sympathetic neurons have been shown with NGF and BDNF, where the former promotes growth via binding to TrKA, and the later inhibits growth via binding to p75.²³

Neurotrophins and the immune system: Neurotrophins such as nerve growth factor (NGF) is synthesised by cells of immune system such as lymphocytes and mast cells, and the level of NGF increases during inflammatory responses while inflammatory cytokines such as interleukin-1 and

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tumor necrosis factor (TNF) are potent inducers of NGF secretion.^{4-8,9,13,14,16} This led to the hypothesis that NGF is involved in the pathophysiology of autoimmune diseases⁷ such as rheumatoid arthritis^{6,16}, systemic lupus erythematosus⁵ and systemic sclerosis.^{7,16}

Acquired immune deficiency syndrome (AIDS) results in a multitude of neurological syndromes as a consequence to neuronal apoptosis but there is no direct invasion of neurocytes by the virus. The invasive strains of HIV infected macrophages, microglial cells and multinucleated giant cells but not neurons as the latter cells lack the appropriate receptors for the virus. It seems that processing of the virus by cells of the myelomonocytic line yields viral products known to initiate a complex work of events that may lead to neuronal apoptosis and to the development of AIDS - associated neurological syndromes. The virus coat protein gp 120 has been proposed to be responsible for initiating these events which lead to apoptosis of neurons, and interaction with signalling by nerve growth factor is one of the major pathological events which results from the presence of gp 120 in the central nervous system.¹⁵ This phenomenon highlights the importance of neurotrophins in maintaining integrity of the nervous system throughout life, and any process which interferes with neurotrophin supply to neurons may lead to degenerative effects on neurons. In the example of AIDS, the immune processing of certain viral products lead to interaction with neurotrophin signalling and result in neuronal apoptosis.

Human immune cells produce neurotrophin 3mRNA, secrete BDNF and express their specific receptors. Truncated trkB receptors expressed in unstimulated Th cells, while full length trkB is expressed in stimulated peripheral blood mononuclear cells (PBMC), B-cell lines and Th-1 but not in Th-2 and Th-0 cell clones. Microbial antigens are known to influence the Th-1/Th-2 balance and hence the neurotrophic pathway. This may have an evolutionary advantage for defence against microbial infection, but it also influences the neuronal synaptic activity of the central nervous system.²⁴

Neurotrophins may play an important role in the regulatory network between the immunological events and the neuronal control of airway hyperactivity in bronchial asthma. This was looked at in human as well as murine models of bronchial asthma. Allergen provocation in mild asthmatics induced airway inflammation which increased local production of NGF and BDNF in mice as well as in humans. Treatment of mice and anti-NGF prevented development of airway hyperactivity. The level of NGF in bronchoalveolar lavage in humans, correlated significantly with baseline FEV1.¹² These data strongly suggest the importance of neurotrophins as molecular links between the

immune system which produce them²⁴ and the neuronal control of airway inflammation in bronchial asthma.¹²

Major histocompatibility complex (MHC) molecules are rare in the healthy brain tissue, but are heavily expressed on microglial cells after inflammatory or degenerative processes. The induction of MHC class II was found to be inhibited by NGF, BDNF or neurotrophin-3, and enhanced by the addition of neurotrophin antagonists.²⁵ Major histocompatibility complex molecules function primarily as antigen - presenter to the immune system. This suggests that neurotrophins secreted by electronically active neurones control the antigen-presenting potential of microglia cells.

The physiological role of neurotrophins is much wider than it was first appreciated. The synthesis of these molecules is not confined to the nervous system and other cells such as those of the immune system also synthesise these molecules and express their appropriate receptors. As well as their original role described in mammalian nervous system, they influence many other biological systems and the immune system is one of these.

Their influences on the immune system include that of antigen-presentation to the immune system and hence response to infection, neuroimmunological interaction in allergic diseases and the resulting inflammation from such interaction, and autoimmune response in connective tissue diseases. Interruption of signalling by neurotrophins is an important pathophysiological process which leads to neuron apoptosis in AIDS. Although the current knowledge concerning neurotrophins has expanded greatly over the past few decades compared to times of initial discovery, there still remains a lot of issues to be addressed and in particular therapeutic manipulations by these agents or their antagonists, especially in neurodegenerative diseases, but also other diseases can be addressed.²⁶⁻²⁸

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