Handbook of Neurochemistry and Molecular Neurobiology

Neuroimmunology

Abel Lajtha (Ed.)

Handbook of Neurochemistry and Molecular Neurobiology

Neuroimmunology

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With 38 Figures and 18 Tables

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Preface

Neuroimmunology is one of the most rapidly developing branches of Neurobiology, prompted by novel neurochemical, neuroendocrinological, and neurophysiological investigations of the central and peripheral nervous system including neuroendocrine systems. Neuroimmunology can be considered as an interdisciplinary science that covers relevant aspects of how the peripheral immune system can influence brain physiology and elicit neuroendocrine immunoregulatory responses and also how local interactions between immune and neuronal mediators of the brain influence the occurrence and course of neuropathologic diseases. Therefore, we have in these volume chapters, focused on immune–neuro–endocrine interactions underlying the control and regulation of processes involved in both immune and brain physiology and in the pathogenesis of different nervous diseases. Among such diseases are: schizophrenia, HIV-associated dementia, rheumatoid arthritis, several experimental pathologies, multiple sclerosis, autoimmune encephalomyelitis, Theilers virus infection, nervous system demyelination diseases, the primary degenerative disorders such as Alzheimer's and Parkinson's as well as brain injuries resulting from stroke and trauma, the neuroimmunology of gene therapy, amyotrophic lateral sclerosis, Prion disease, and all theoretical questions covering these pathologies. All of the above-mentioned involve autoimmune processes.

It is difficult, indeed, to imagine fundamental neurobiological processes, autoimmune, neuroendocrine, and infectious diseases, where immune factors are not of prime importance. The elucidation of the intimate molecular-biological problems of immunopathologies requires deep knowledge of the intricate connection between immunomodulators, immune competent cells of blood, brain, and other organs.

This volume contains data on multiple immunomodulators, many of which are also the products of hypothalamic brain cell neurosecretion. Interleukins (IL-1α, IL-1β, IL-2, IL-4, IL-6, TNFα), immunophylin and ubiquitin as well as proline-rich peptides, comprised of 10–15 amino acids are being produced in Nucleus supraopticus and Nucleus paraventricularis and then secreted into neurohypophysis. Along the neurosecretion of the mentioned cytokines, there are other immunomodulators, the primary structure of which had been completely deciphered such as: Immunophyllins, intracellular receptors of immunosuppressors FK506, cyclosporine A, rapamicin. They are peptidyl-prolyl-*cis–trans*-isomerases. There are novel immunological hypothalamic factors such as ubiquitin, macrophage migration inhibitory factor (MIF), as well as Thymosin β_4(1–39). The latter is the activator of Ca^{2-}calmodulin dependent enzymes without Ca^{2+} and calmodulin participation. These data allowed us to propose the concept of neuroendocrine immune system of the brain (A. Galoyan, Chapter 7).

The new compounds participating in immune response are poly (ADP-ribose) polymerase (C. Szabo, Chapter 20) and immunoproteasome in the nervous system (M. Rinaudo and M. Piccinini, Chapter 9). Polymerase (PARP-1) is a DNA-binding protein and is involved in the control of DNA metabolism. PARP-1 is involved in the upregulation of numerous proinflammatory genes that play a pathogenic role in the later stage of central nervous system (CNS) diseases. Immunoproteasome is a nonlysosomal ubiquitin-dependant protease. The proteosome activity is essential in a wide range of vital cellular processes extending from cell division and differentiation, DNA repairing, transcription factor and regulatory protein processing, membrane receptor internalization, inflammatory response and antigen presentation.

The intimate interaction of neurons and immune cells is of fundamental theoretical importance, bringing attention to the neural and immune activity of the same brain cells. The discovery that "brain-born" cytokines are induced during hippocampal long-term potentiation was important to prove that these mediators, when released at low levels as a consequence of increased neural activity, are involved in physiologic functions of the CNS such as synaptic plasticity and memory consolidation. Data documenting

this aspect, which is incorporated to the conceptual framework that a network of immune–neuro–endocrine interactions operates during health and disease, is the main subject of Chapter 1: "Brain Cytokines as Integrators of the Immune–Neuroendocrine Network" (H. Besedovsky and A. del Rey). In Chapter 6: "Neuro-immune associative learning" (Niemi M.B et al) the idea of afferent and efferent pathway of brain-immune communications is further developed, focusing on the immune response change under the stimuli of conditioned and unconditioned reflexes. Also the fact that certain immune processes can be behaviorally conditioned is indicative of an active exchange of information between the immune and nervous systems (Chapter 6).The influence of the CNS mediators on immunocompetent cells is also illustrated for example by effects of the endogenous purine nucleoside eadenosine that express four subtypes of adenosine receptors (A_1, A_2, $A_{2b,}$ and A_3). These receptors are expressed on cells of the brain immune system (G. Hasko and E.S. Vizi, Chapter 12).

There is clear information documenting effects of neurotransmitters on the immune system. Serotonin regulates the hematopoiesis immunocompetent cells and that of bone marrow. The serotonin in blood is stored in the dense granules of platelets. Serotonin has marked activities on inflammation and immunity, affecting almost all the types of mature blood cells. Of interest are reports on the cytokine effects, produced in peripheral immunocompetent cells on brain neurochemistry (A. Dunn, Chapter 3). The most studied effect is the capacity of this cytokine to activate the hypothalamo-pituitary-adrenocortical (HPA) axis. Interrelationship between peripheral and brain immune system, including innervation of immune organs and tissues, are examined. Of interest is the innate immune system of brain that is commonly affected by mediators and transmitters derived from both neurons and immune cells of the brain and the similarities between neuronal and immune synapses. There are clear data on peripheral cytokines, hormones, together with mediators of the immune system on the brain, can affect specifically neuroendocrine and behavioral mechanisms and responses (G. Juhasz, Chapter 13). These data further reinforce the relevance of the neuroimmune cross talk. A. Rostami (Chapter 16), discusses experimental autoimmune encephalomyelitis (EAE) (animal model of multiple sclerosis), where antigen-presenting cells, primed autoreactive CD4+ T cells, react against myelin components and migrate in the brain (through the blood-brain barrier, which is reactivated by microglia and present myelin peptides), triggering in this way processes that cause autoimmune demyelination. The understanding of the origin of autoimmune diseases in the brain as well as the treatment of those diseases, represent an important task for Neuroimmunology (D. Jessop, Chapter 2). EAE is a well-characterized disease of CNS (C. Welsh and C. Young, Chapter 15). One chapter is dedicated to the treatment of the autoimmune diseases "Drugs and target sympathetic-immune pathways for treatment of autoimmune diseases" (D. Lorton, Chapter 5), characterized by immune system dysregulation of nervous stress pathways, the sympathetic nervous system, and the hypothalamic-pituitary-adrenal axis. This chapter summarizes changes that occur in sympathetic to immune signaling in autoimmune diseases using rheumatoid arthritis as a specific example and presenting similarities of other autoimmune diseases. The potential drugs for the treatment of autoimmune diseases targeting sympathetic nervous system are considered. Among the diseases considered as autoimmune are: encephalomyelitis, paraneoplastic encephalomyelitis, autoimmune neurological disorders. Autoimmune diseases can be induced by intracellular vesicle-associated proteins, multiple sclerosis, several neurodegenerative diseases, etc. They are all subjects for the brain immune system studies, each one of them has specific mechanism. A few chapters are dedicated to the inflammatory components in different brain pathologies and infection. Inflammation is a key component in the immunological defense of organism against health-threatening pathogens. Dysregulation of inflammatory response can lead in turn to tissue damage and subsequently to disease. An immunosuppressive environment is mainly responsible for the characteristic features of the inflammatory responses in CNS. Inflammation is now known to have toxic and protective effects in neurodegenerative diseases such as Parkinson's, Alzheimer's, and Prion diseases; microglial activation appears as a common feature to all those pathologies (F. Pitossi, Chapter 18). Neuroinflamation is a pathological condition of the CNS that happens in response to invasion of a multitude of infectious pathogens and also in autoimmune diseases. There is a great variation in susceptibility to specific infectious agents in human and mouse CNS reflecting genetic predispositions. The CNS is not dependent on resident tissue leukocytes or infiltrating macrophages or neutrophils to recognize and clear pathogens. Instead, the CNS has established its own immune system, based on activation of resident innate immune cells such as microglia or astrocytes

(W. Stenzel and G. Alber, Chapter 10; N. Bhat, Chapter 14). Inflammation takes place in HIV associated dementia (J. Tan, Chapter 19). Immunological aspects of CNS demyelination are discussed in Chapter 17 (S. Sriram and S. Pawate).

Special chapters review our understanding of how normal aging alters the cross talk between the autonomic nervous system and the immune system to alter immune functions with age (D. Bellinger et al., Chapter 4) and the neuroimmunology of gene therapy using the virus vectors for the treatment of neurological diseases (P. Lowenstein et al., Chapter 11). Numerous preclinical and clinical gene transfer studies have been carried out using viral vectors modified from pathogenic viruses or artificial nonviral liposome-based approaches. In this volume, we discuss immune response during Schizophrenia (F. Gaughran and J. Welsh, Chapter 21). However, at present time it is very difficult to define the interrelationship between the brain immune system and the pathogenesis of complicated systems.

For the first time the neuroimmunological, neurophysiologic, and neurochemical aspects of neuro–immune interactions are broadly discussed by worlds leading neurobiologists. We hope that this unusual multidimensional association would serve to increase the understanding of the relevance of neuro–endocrine–immune networks during health and disease.

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Table of Contents