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Physiology and Pathology of Neuroimmunology: Role of Inflammation in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a neurodegenerative disease that affects 1% of the population aged 65 and over and is the second most common neurodegenerative disease next to Alzheimer's disease. Interneuronal proteinaceous inclusions called Lewy bodies (LB) and a selective degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNPC) are the main features of PD pathology. The most common clinical manifestations are rigidity, tremor, bradykinesia, postural instability, sleep disorders, alterations in gait, smell, memory, and dementia. Genetic and environmental factors are involved in PD, and, recently, oxidative stress, proteasome-mediated protein degradation, and inflammation have acquired relevance as major mechanisms of neuronal dysfunction. Increased levels of reactive oxygen and nitrogen species in the brain contribute to greater vulnerability of proteins to nitro-oxidative modification and to greater degrees of aggregation. These protein aggregates contain a variety of proteins of which α-synuclein appears to be the main structural component. Interestingly, α-synuclein can be secreted by neuronal cells and may lead the initiation and the maintenance of inflammatory events through the activation of microglia, which contributes to dopaminergic neuron depletion. New evidence also suggests that PD may be the result of an autoimmune response in which the immune cells recognize the neurons as foreign elements and would act against them, causing their death.

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1. Introduction

The central nervous system (CNS) has traditionally been considered immunologically privileged due to the protection conferred by the blood-brain barrier; it lacks lymphatic vessels and is devoid of dendritic cells, and the parenchyma cells do not express major histocompatibility complex (MHC) class-I antigen-presenting molecules. However, the CNS can modulate the immune response and limit inflammation-induced tissue damage [1]. Neurons of the CNS are actively involved in control of the immune response by modulating the function of glial cells and T lymphocytes. There are mechanisms involved in the control of the immune response: the direct contact through membrane glycoproteins (CD22, CD47, CD200), neural cell adhesion molecules (NCAM or CD56), intercellular cell adhesion molecule-1 (ICAM-1), semaphorins and cadherins, and the mechanism independent of cell-cell contact that involves the expression of the Fas ligand or CD95L, which promote apoptosis of microglial cells and T lymphocytes. The immune system is not a completely autonomous system since the lymphoid organs are innervated by cholinergic, catecholaminergic, and peptidergic neurons and other neurons [2]. Thus, the nervous system and the immune system can interact not only through the hypothalamic-pituitary-adrenal axis, whose activation leads to the synthesis of corticosteroids that inhibit the immune response, but can also do so through neuronal circuits at the central level through the autonomic nervous system (ANS), both sympathetic and parasympathetic, which, through sensory and effector circuits, transmit impulses that reflexively induce the implementation of an anti-inflammatory response. In physiological conditions, the sensory and afferent fibers of the ANS travel in the vagus nerve from the peripheral tissues to the CNS to provide information about tissue function or, on the contrary, about the existence of injury within tissues that leads to the development of a cytokine-induced inflammatory process. The afferent sensory stimulus triggers a response in the CNS that includes the signs and symptoms of the disease and the efferent sympathetic pathway, called the cholinergic anti-inflammatory reflex, which, through the vagus nerve, inhibits the synthesis of pro-inflammatory cytokines and thus limits or prevents tissue damage produced by these mediators.

Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, produced during the activation of innate immunity cells in peripheral tissues, are able to modulate the activity of CNS neuronal circuits through specific receptors expressed by neurons of the hypothalamus and other regions of the brain. In this way, a response is characterized by the transmission of action potentials that trigger local and systemic symptoms and signs of the disease syndrome, which are then controlled by the cholinergic and anti-inflammatory vagal route. This CNS response leads not only to control the progression of the inflammatory process in the peripheral tissue but also to prevent eventual immune-mediated tissue damage. Thus, the immunological activation of this neuronal circuit confers protection against tissue damage by inhibiting the release of cytokines during infection, autoimmunity, shock, and other inflammatory syndromes in the CNS.

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