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Cytokines and brain excitability: Molecular Mediators.

Diego Fernando Alegría Portilla, MD

Jhan Sebastián Saavedra-Torres, MD

Tomas Omar Zamora Bastidas, MD

Luisa Fernanda Zúñiga Cerón, MD

Vanessa Perdomo Galviz, MD

Beatriz Andrea Rengifo Ordoñez, MD

Diana Marcela Pino Terán, MD

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Cell Activation: brain excitability

Because of the compartmentalization of disciplines that shaped the academic landscape of biology and biomedical sciences in the past, physiological systems have long been studied in isolation from each other (1).

This has particularly been the case for the immune system. As a consequence of its ties with pathology and microbiology, immunology as a discipline has largely grown independently of physiology. Accordingly, it has taken a long time for immunologists to accept the concept that the immune system is not self-regulated but functions in close association with the nervous system. These associations are present at different levels of organization. At the local level, there is clear evidence for the production and use of immune factors by the central nervous system and for the production and use of neuroendocrine mediators by the immune system (1).

Shortrange interactions between immune cells and peripheral nerve endings innervating immune organs allow the immune system to recruit local neuronal elements for fine tuning of the immune response. Reciprocally, immune cells and mediators play a regulatory role in the nervous system and participate in the elimination and plasticity of synapses during development as well as in synaptic plasticity at adulthood (1).

Cell activation is a major element in the brain reaction to injury, whereas local neural cells and peripherally derived immune cells participate (3). In effect, resident cells (particularly astrocytes and microglia) undergo hypertrophy and proliferation. Migrant immune cells from the circulation include mononuclear phagocytic macrophages (2), T cells, and NK cells, but polymorphonuclear leukocytes could be prominent early, particularly when damage involves necrosis or hemorrhage (2,4).

Microglia are resident cells of the brain involved in regulatory processes critical for development, maintenance of the neural environment, injury and repair. They belong to the monocytic-macrophage lineage and serve as brain immune cells to orchestrate innate immune responses; however, they are distinct from other tissue macrophages due to their relatively quiescent phenotype and tight regulation by the CNS microenvironment (4,5).

Microglia actively survey the surrounding parenchyma and respond rapidly to changes such that any disruption to neural architecture or function can contribute to the loss in regulation of the microglia phenotype. In many models of neurodegeneration and neurotoxicity, early events of synaptic degeneration and neuronal loss are accompanied by an inflammatory response including activation of microglia, perivascular monocytes, and recruitment of leukocytes (5).

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In culture, microglia have been shown to be capable of releasing several potentially cytotoxic substances, such as reactive oxygen intermediates, nitric oxide, proteases, arachidonic acid derivatives, excitatory amino acids, and cytokines; however, they also produce various neurotrophic factors and quench damage from free radicals and excitotoxins. As the primary source for pro-inflammatory cytokines, microglia are implicated as pivotal mediators of neuroinflammation and can induce or modulate a broad spectrum of cellular responses (5,6).

Inflammation plays an important role in the pathogenesis of ischemic stroke:

Neuroinflammation should be considered as a balanced network of processes whereby subtle modifications can shift the cells toward disparate outcomes (5). Microglia make up the innate immune system of the central nervous system and are key cellular mediators of neuroinflammatory processes. Their role in central nervous system diseases, including infections, is discussed in terms of a participation in both acute and chronic neuroinflammatory responses. Specific reference is made also to their involvement in Alzheimer's disease where microglial cell activation is thought to be critically important in the neurodegenerative process (5,6).

Inflammation plays an important role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury (6). The role of molecular mediators in driving the immunoinflammatory processes is pivotal in brain injury. Increasing evidence suggests that inflammatory response is a double-edged sword, as it not only exacerbates secondary brain injury in the acute stage of stroke but also beneficially contributes to brain recovery after stroke (6,7).

Ischemic stroke is one of the most frequent causes of injury to the central nervous system. It is now increasingly clear that human stroke causes multi-organ systemic disease. Brain inflammation may lead to opposing local and systemic effects. Suppression of systemic immunity by the nervous system could protect the brain from additional inflammatory damage; however, it may increase the susceptibility to infection. Pneumonia and urinary tract infection are the most common complications occurring in patients after stroke (8).

The mechanisms involved in lung-brain interactions are still unknown, but some studies have suggested that inhibition of the cholinergic anti-inflammatory pathway and release of glucocorticoids, catecholamines, and damage-associated molecular patterns (DAMPs) are among the pathophysiological mechanisms involved in communication from the ischemic brain to the lungs after stroke (7,8).

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Inflammation plays an important role in the pathogenesis of ischemic stroke and other forms of ischemic brain injury (6). Although several approaches for anti-inflammatory treatment have proven effective for treating acute stroke in animal models, none of these treatments has proven effective in clinical trials (7). Increasing evidence suggests that inflammatory response is a double-edged sword, as it not only exacerbates secondary brain injury in the acute stage of stroke but also beneficially contributes to brain recovery after stroke. Undoubtedly, there is still much to be done in order to translate promising pre-clinical findings into clinical practice (6).

Cytokines and fever

Activated cells thus produce cytokines, chemokines, adhesion molecules (AMs), growth fac- tors (GFs), and other biological mediators that become implicated in complex intermolecular interactions involving numerous networks. There is also an associated blood-brain barrier (BBB) dysfunction whereby a leaky state promotes transendothelial migration of immune cells. Increased permeability also contributes to edema and intracranial hypertension (9).

These changes contribute to CNS inflammation and could trigger other cellular and molecular changes, often associated with expression of major histocompatibility (MHC) antigens. Physiopathological alterations affect cerebral oxygenation and blood or nutrient supplies, with resultant biochemical and metabolic dysregulations (9).

According to the classical view, fever develops in a characteristic sequence of steps starting with the appearance of the pathogenic agent, the "exogenous pyrogen" in the afflicted host (10,11).

This exogenous pyrogen causes the release of fever-producing substances by the host's polymorphonuclear leukocytes and by other cells. These substances are called "endogenous pyrogens". Fever is an excellent example of neuroimmunomodulation in those mediators of immunity initiate a pathway to raise the thermoregulatory set-point, resulting in behavioral and physiological responses that increase body temperature (10,11).

This rise in temperature is thought to be adaptive, facilitating host defenses. Many cytokines are endogenous mediators of fever (i.e., endogenous pyrogens), including interleukin (IL)-, 1 beta, IL-6 and others (10). Tumor necrosis factor-alpha may be both an endogenous pyrogen and an endogenous antipyretic or cryogen, depending on the nature of the inflammatory stimuli. Although there is evidence that cytokines within the hypothalamus initiate fever, recent findings indicate that the signal to increase these brain cytokines may be neural (i.e., from peripheral nerves), rather than humoral (i.e., circulating endogenous pyrogen) (10,11).

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The contribution of astrocytes and microglia to traumatic brain injury

Pathophysiology of TBI. Damages of neuronal tissues associated with TBI fall into two categories: (i) primary injury, which is directly caused by mechanical forces during the initial insult; and (ii) secondary injury, which refers to further tissue and cellular damages following primary insult. Despite dramatic improvements in the management of traumatic brain injury (TBI), to date there is no effective treatment available to patients, and morbidity and mortality remain high (12).

The damage to the brain occurs in two phases, the initial primary phase being the injury itself, which is irreversible and amenable only to preventive measures to minimize the extent of damage, followed by an ongoing secondary phase, which begins at the time of injury and continues in the ensuing days to weeks. This delayed phase leads to a variety of physiological, cellular, and molecular responses aimed at restoring the homeostasis of the damaged tissue, which, if not controlled, will lead to secondary insults. The development of secondary brain injury represents a window of opportunity in which pharmaceutical compounds with neuroprotective properties could be administered. To establish effective treatments for TBI victims, it is imperative that the complex molecular cascades contributing to secondary injury be fully elucidated (12).

One pathway known to be activated in response to TBI is cellular and humoral inflammation. Neuroinflammation within the injured brain has long been considered to intensify the damage sustained following TBI. However, the accumulated findings from years of clinical and experimental research support the notion that the action of inflammation may differ in the acute and delayed phase after TBI, and that maintaining limited inflammation is essential for repair. This review addresses the role of several cytokines and chemokines following focal and diffuse TBI, as well as the controversies around the use of therapeutic anti-inflammatory treatments versus genetic deletion of cytokine expression (12).

Besides neurotrauma and ischemia, injury to the brain can result from other insults to the CNS, such as infections, autoimmune and neurodegenerative diseases, perinatal leukoencephalopathy, toxic or metabolic disorders, and several other conditions (11,13). Like other organs, the brain reacts to injury or disease by cascades of cellular and molecular responses. Astrocytes play key roles in this process. Astrocytes can both respond to and produce many immunomodulatory molecules, including cytokines, chemokines and inflammatory mediators such as danger-associate molecular patterns (DAMPs) and alarmins released by stressed, injured or dying cells (11,13).

Each of the populations of non-neuronal cells of the adult CNS are remarkably adapted to support neuronal function: astrocytes maintain ionic and neurotransmitter homeostasis, refine synaptic connections (15), and provide neuronal metabolic substrates; microglia monitor synaptic elements and networks (13).

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Any type of tissue injury in the central nervous system (CNS) is associated with local changes in the microenvironment, which are in part similar to those seen in inflammatory conditions. Cell injury in the CNS results in activation of microglia and astrocytes. Furthermore, a similar activation of microglia can be induced even by functional changes in neuronal networks, such as for instance sustained overactivation of neuronal circuits in epileptic seizures. Activation of glia is induced by different signals, including release of adenosine triphosphate (ATP) and its signaling through G-protein coupled (13).

Receptors, by direct neurotransmitter signaling or by the liberation of intracellular components from damaged cells, resulting in the activation of pattern recognition receptors. An important consequence of astrocyte and microglia activation is the production of a wide spectrum of pro- and anti-inflammatory cytokines and growth factors. Thus, microglia and astroglia activation as a reflection of an inflammatory response to tissue injury may have beneficial as well as detrimental consequences for adjacent neurons and glia, depending on the type of the primary tissue injury and on the properties of the environment where it takes place (13).

The inflammatory response is critical to fight insults, such as pathogen invasion or tissue damage, but if not resolved often becomes detrimental to the host (14,15). A growing body of evidence places non-resolved inflammation at the core of various pathologies, from cancer to neurodegenerative diseases. It is therefore not surprising that the immune system has evolved several regulatory mechanisms to achieve maximum protection in the absence of pathology. The importance of the innate immune cells of the CNS to maintain the brain homeostasis is now fully accepted. In this context, the instrumental role of microglia for brain development and functionality is unquestionable (14).

Whether microglia activation is also instrumental for pathogen elimination, or whether mononuclear cells from the periphery do this job, remains unclear. In any case, the immune response triggered in the brain is critical to restore homeostasis upon injury (15). However, above a certain threshold, the initially immune-protective response may become immune-degenerative, by causing tissue damage (16). Given the demonstrated potential of IL-10 in modulating brain inflammatory settings, it is of major importance to understand how IL-10 production is regulated in innate immune cells of the CNS and how it impacts inflammatory responses in this compartment (15,16).

Thus, unveiling the common and the cell-specific mechanisms regulating IL10 production in different settings and by different cellular populations will open new avenues for the development of specific targets to effectively and efficiently modulate IL10 (15,16).

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Conclusions

The importance of the innate immune cells of the CNS to maintain the brain homeostasis is now fully accepted. In this context, the instrumental role of microglia for brain development and functionality is unquestionable. Cell activation is a major element in the brain reaction to injury, whereas local neural cells and peripherally derived immune cells participate. Cytokines are molecules secreted by peripheral immune cells, microglia, astrocytes and neurons in the central nervous system. Peripheral or central inflammation is characterized by an upregulation of cytokines and their receptors in the brain. Emerging evidence indicates that pro-inflammatory cytokines modulate brain excitability.

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