

## Brain Involvement in Peripheral Inflammatory Disease

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### Pathogenesis of Inflammatory Disease

The immune system undergoes complex biological processes to protect the body from pathogens, and other potentially harmful substances such as damaged cells or irritants. This immune response mechanism of the body is known as inflammation. The primary purpose of the inflammatory mechanism is to remove the injurious agent and initiate a healing process for the tissue. Even though not an infection, inflammation can be caused by an infectious pathogen [1,2].

In the absence of a harmful agent, the immune system could trigger an inflammatory response. This is known as auto-immune response, and it results in the release of white blood cell chemicals that otherwise become harmful to the tissues of the body. The initial inflammatory response increases the movement of plasma and leukocytes from the blood into the injured tissues; this is known as acute inflammation. A cascade of biochemical events may occur and translate the acute response into chronic inflammation which progressively changes the type of cells within the site of the inflammation [3]. Chronic inflammation is characterized by the simultaneous destruction and healing of tissues, which can result in a host of diseases such as rheumatoid and psoriatic arthritis [2-4].

### Involvement of the central nervous system (CNS) in inflammatory disease

Apart from immune cells, non-immune cells such as epithelial cells, endothelial cells and fibroblasts also contribute to inflammatory processes [2]. Inflammatory pathways and their target tissues vary widely depending on the nature of stimulants. In the presence of bacterial infection, the immune cells through specific receptors immediately sense pathogens. Activation of pathogen-specific receptors induces the production of inflammatory mediators such as inflammatory cytokines [e.g. tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6)] and chemokines. These mediators rapidly accelerate the progression of inflammation by modifying the permeability of vascular endothelial tissues; they also direct neutrophils and excess plasma into the site of infection. At the same time, the invading pathogens are targeted and destroyed by the immune cells [2,5].

The inflammatory response may extend toward systemic effects through the excessive production of pro-inflammatory cytokines, which mediate the secretion of acute phase proteins by the liver cells [2]. These proteins, in turn, induce brain endothelium and facilitate the production of prostaglandins, which are primarily responsible for the onset of symptoms (of inflammatory disease) through their effects on the central nervous system.

### Effect of anti-inflammatory therapy on brain chemistry and mood

Animal studies [6,7] have shown that peripheral immune cells access the brain through humoral and/or neural routes, resulting in central neural changes and associated behavioral alterations. It is believed that TNF- $\alpha$  (a pro-inflammatory cytokine) signaling initiates this peripheral-CNS communication process [2,6,7]. TNF- $\alpha$ , which is a peripheral cytokine, stimulates microglia to produce the harmful protein molecules that access the brain through a number of ways including crossing the blood brain barrier [5,8]. This compromised defensive function of the brain may lead to chronic inflammation. Therefore, any form of anti-TNF- $\alpha$  therapy targeted at inhibiting microglial activation, or blocking the receptors of microglia could reverse the communication pathway between the CNS and the periphery, and reduce the physiological and behavioral impacts of peripheral inflammation [5-9].

The inflammatory-related physiological changes in the CNS have been reported by brain imaging studies [10-12] to be associated with under-activation of the forebrain structures (notably the dorsolateral prefrontal and anterior cingulate cortices) and over-activation of the limbic structures (notably the hippocampus, amygdala, insula and thalamus). Using proton magnetic resonance spectroscopy (1H-MRS) techniques [13-17], this activation pattern has been observed to correlate with changes in brain chemistry of these brain regions. The consequence of these physiological alterations in these brain regions might explain the associated behavioral changes over time.

### Conflict of Interest

The author has no conflict of interest.

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