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Review article

Neuroinflammation: The role and consequences

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ABSTRACT

Neuroinflammation is central to the common pathology of several acute and chronic brain diseases. This review examines the consequences of excessive and prolonged neuroinflammation, particularly its damaging effects on cellular and/or brain function, as well as its relevance to disease progression and possible interventions. The evidence gathered here indicates that neuroinflammation causes and accelerates long-term neurodegenerative disease, playing a central role in the very early development of chronic conditions including dementia. The wide scope and numerous complexities of neuroinflammation suggest that combinations of different preventative and therapeutic approaches may be efficacious.

Contents

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; CDK5, cyclin-dependent kinase 5; CNS, central nervous system; COX, cyclooxygenase; CRP, C-reactive protein; FADD, Fas-Associated protein with Death Domain; GSK3, glycogen synthase kinase-3; IFN-γ, interferon-γ; IL, interleukin; IL-1β, interleukin-1beta; iNOS, nitric oxide synthase; LPS, lipopolysaccharide; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase pathways; NO, nitric oxide; NPCs, neural progenitor cells; NSAIDs, non-steroidal anti-inflammatory drugs; PAMPs, pathogen-associated molecular patterns; POCD, postoperative cognitive dysfunction; SGZ, subgranular layer; TLRs, toll-like receptors; TNF, tumour necrosis factor; TRADD, tumour necrosis factor receptor type 1-associated Death domain protein; TRAIL, tumour-necrosis-factor-related-apoptotic-ligand.

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1. Introduction

Inflammation is a response of the innate immune system that aims to protect and defend the body. Triggers can be an aseptic insult such as sterile surgery (where tissue damage caused by mechanical injury induces an inflammatory response), or non-aseptic (such as bacterial or viral invasion). The inflammatory response is orchestrated by the mobilisation and interaction of several cell types and signalling molecules, producing a response that is both local and systemic. The cell types central to the inflammatory response are white blood cells (leucocytes) and endothelial cells. Leucocytes, including monocytes, are derived from the mononuclear phagocyte system (bone marrow, lymph nodes and spleen) and can penetrate tissue where their functions include phagocytosis and antigen presentation. Signalling molecules include locally acting small molecules such as nitric oxide (NO), lipid compounds, e.g. prostaglandins and complex circulating proteins, cytokines. Innate immunity comprises of generic, non-specific responses of the immune system, usually triggered by distinctive pathogen-derived molecules known as pathogen-associated molecular patterns (PAMPs). This is an immediate, and often short-lived, response. This differs from the adaptive immune response, which involves T and B lymphocytes, begins to take effect two to three weeks following infection and produces a highly specialised response to pathogens. Processes such as somatic hypermutation enable a relatively small number of genes to encode a huge array of receptors.

Initially, tissue resident leucocytes stimulate endothelial cells to present cellular adhesion molecules that recruit more leucocytes to the site of tissue damage. Adhesion molecules weakly bind circulating leucocytes, slowing them down and enabling their adherence to signalling endothelium. Such endothelium undergoes a phenotypic change becoming permeable to the leucocytes that are drawn towards a high concentration of cytokine near the stimulus. Within the tissue, monocytes differentiate to macrophages capable of phagocytosis and secretion of further signalling molecules, which mobilise and recruit more effector cells from the periphery. Thereby the inflammatory response is maintained and amplified, spreading from a local focus to a systemic response.

Inflammation aims to clear and control the initial stimulus, for example, through phagocytosis and activation of the inflammasome (which triggers apoptosis (Fernandes-Alnemri et al., 2009)), to ultimately enable tissue regeneration and scarring. However, although intended to be protective and beneficial, an excessive inflammatory response can cause or contribute to tissue damage and disease pathology. Once deployed, activated cells target not only the initial site of inflammation, but also remote sites that are responding to the inflammatory stimulus.

Peripheral inflammation triggers a neuroinflammatory response involving blood–brain barrier, glia and neurons. Neuroinflammation is a term used to describe the broad range of immune responses of the central nervous system, differing from peripheral inflammation in a number of ways, primarily concerning the principle cells involved (such as microglia and astrocytes). The blood brain barrier, a highly specialised form of endothelium, was previously thought to completely separate the central nervous system from the peripheral immune system. However, it is not only permeable to pro-inflammatory mediators derived from peripheral inflammation, but can also be stimulated to both release and transmit these mediators and allow leucocyte migration into the brain (de Vries et al., 1996; Laflamme et al., 1999). This neuroinflammatory response results in synaptic impairment, neuronal death and an exacerbation of several disease pathologies within the brain (Cunningham et al., 1996; Kitazawa et al., 2005; Micheau and Tschopp, 2003).

This review will focus on the consequences of excessive and prolonged neuroinflammation, particularly its damaging effects on brain function. Its relevance to disease progression, ranging from acute conditions including delirium and postoperative cognitive dysfunction to chronic diseases such as Alzheimer's disease and multiple sclerosis, will be explored briefly, along with possible interventions. The evidence gathered here suggests that neuroinflammation causes and accelerates long-term neurodegenerative disease, playing a central role in the very early development of chronic conditions including dementia. The wide scope and numerous complexities of neuroinflammation suggest that combinations of different preventative and therapeutic approaches may be efficacious.

2. Neuroinflammation

2.1. Cellular components of neuroinflammation

The endothelial layer known as the blood–brain barrier (BBB) and transport of molecules across it is key to understanding how peripheral inflammation can cause prolonged and damaging neuroinflammation. Inflammatory cytokines and other proteins were originally thought to be too large to enter the brain from the blood, but a number of transport mechanisms have come to light over the last two decades. BBB active transport systems have been observed facilitating the delivery of TNF and IL cytokines into the brain (Gutierrez et al., 1993). Circumventricular organs, which have an incomplete barrier at the blood–brain interface, are particular areas of concentrated cytokine transport (Quan et al., 1999). TNF-α, IL-6, IL-1β and other cytokines also have adverse affects on the integrity of the BBB, allowing it to become more permeable and enabling the entry of leucocytes into the brain (Laflamme et al., 1999; Terrando et al., 2011). Cytokine levels are known to modulate the permeability of the BBB by altering the resistance of tight junctions in endothelial cells in brain vasculature (Wong et al., 2004), high levels up-regulating inflammatory cytokines and COX-2 transcription in the endothelium (de Vries et al., 1996). Damage to integral tight junction proteins such as occludin results in an increased tight junction permeability, possibly through affecting its interaction with the cell cytoskeleton. Vagal stimulation by peripheral cytokines has direct influence on the central nervous system (CNS) and induces sickness behaviour (Goehler et al., 1999) and this presents another interesting area in the translation of peripheral inflammation to neuroinflammation, as recently reviewed (Fung et al., 2012). The movement of leucocytes across the BBB is also regulated to some extent by other humoral factors such as chemokines. For example, chemokines CCL19 and CCL21 enable T cell adhesion to the BBB, whereas CXCL12 may play a pivotal role in reducing T cell infiltration (Engelhardt., 2010). Many of these humoral factors are produced by astrocytes, and upregulation of molecules produced by these glial cells have important effects on the integrity of the BBB. An example is shown in bradykinin triggering the release of IL-6 from astrocytes during inflammation (Schwaninger et al., 1999).