Neurodegeneration: Microglia: Nf-Kappab Signaling Pathways

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ABSTRACT

Microglia is cells of mesodermal/mesenchymal origin that migrate into the central nervous system (CNS) to form resident macrophages inside the special brain microenvironment. Intact with both neuronal and non-neuronal cells, microglia is highly active cells. Continuous process extension and retraction allows microglia to scan the brain parenchyma for threats. They are also able to change their morphology from ramified to amoeboid, which is a sign of cell activity. In response to pleiotropic stimuli such as neurotransmitters, cytokines, and plasma proteins, microglia express a diverse range of receptors. As controllers of synaptic activities and phagocytosis of developing neurons, they serve a critical role in the healthy brain and have significant effects on synaptic plasticity and adult neurogenesis. A frequent cause of hypoparathyroidism is a mutation in the gene glial cells missing-2 (GCM2). Neonatal hypoparathyroidism has an amorphic recessive GCM2 mutation, while autosomal dominant hypoparathyroidism has a dominant-negative GCM2 mutation. Curiously, familial isolated hyperparathyroidism has been associated with activating GCM2 mutation. In addition to seizures, neurocognitive impairment, carpopedal spasm, tingling and numbness are common clinical manifestations of hypoparathyroidism. Biogenic amines are a group of four neurotransmitters that belong to that category and these include serotonin, dopamine, norepinephrine, and epinephrine. Numerous antidepressants prevent the reuptake from occurring the brain-gut axis is hardwired through the CNS, enteric nervous system (ENS), neuroendocrine linkages and highly innervated nerve plexuses.

Introduction

Studies in neuropathology and neuroradiology show that neuroinflammation in some neurodegenerative illnesses may be discernible years before there is a major loss of neurons and bacterial infections that cause widespread inflammation [1]. Nuclear factor kappa B (NF-κB) and activated protein-1 (AP-1) are transcription factors that control the gene expression of various cytokines, chemotactic, and matrix proteins involved in inflammation, immune responses, and cell proliferation Numerous genes implicated in the development of renal illness, including the chemokines likes monocyte chemoattractant protein-1 (MCP-1) and regulated on activation normal T-cell expressed and secreted (RANTES). Reperfusion arrhythmias are caused by intricate cellular and humoral processes that occur when a blocked coronary artery is opened [2]. Experiments that subjected the hearts of large animals to varied periods of coronary artery closure followed by reperfusion provided early insights into the circumstances that generate reperfusion arrhythmias [3]. When the ischemia duration was increased from five minutes to 20 or 30 minutes in these tests, it was shown that the incidence of reperfusion-induced ventricular fibrillation rose. When reperfusion was delayed for longer than 30 to 60 minutes, on the other hand, the incidence of reperfusion-induced ventricular fibrillation decreased [4]. These studies also discovered that severe arrhythmias that formed during the ischemia period were associated with higher incidences of reperfusion-induced ventricular fibrillation. Enhanced intracellular glucose transport and oxidation leads to mitochondrial overproduction of superoxide [5]. This can, in turn, activate other superoxide production pathways that may amplify the original damaging effect of hyperglycemia. Microglias in the CNS are known to become activated by systemic inflamma-

tion, and it has been hypothesized that these cells help neurodegenerative disorders [6]. Neurodegeneration in experimental animal models can be induced or even exacerbated by systemic intraperitoneal administration of bacterial lipopolysaccharides (LPS) in a single or recurrent exposure [7]. It has been demonstrated that, in an animal model of prion disease, systemic administration of a single dose of 100 mg LPS per gramme body weight (gbw) communicated to the brain and caused behavioral changes, microglial activation, and local production of inflammatory cytokines that aided in neurodegeneration. Additionally, mice given a single systemic LPS (5 g/gbw, i.p.) injection showed loss of dopaminergic tyrosine hydroxylase (TH)-positive neurons in the substantia nigra (SN) [8]. Loss of TH-positive neurons in the SN was seen in parkin-deficient mice after 3 months of intraperitoneal challenges with 750 EU/gbw LPS, although this was not seen in control-treated parkin-deficient mice until 6 months after the initial challenge. As a result, it can be concluded from all of these investigations that dopaminergic neurons in the SN are vulnerable to inflammatory damage following systemic LPS exposure, while the precise molecular mechanism behind neurodegeneration is unknown [9]. In this study, we compared the outcomes of a single and repeated injection of systemic LPS in mice [10]. We found that the repeated administration of LPS led to the degeneration of dopaminergic neurons in the SN by inducing a unique, sustained inflammatory microglial phenotype with enrichment of the complement-phagosome pathway. Dopaminergic neurons are lost because of their striking responses to the pathophysiology of the disease, microglia, the immune cells of the central nervous system, have long been a focus of research in the field of Alzheimer's disease (AD) [11]. The potential significance of these cells has never been more apparent given the recent influx of extensive genetic studies linking microglial chemicals to AD [12]. It may not come as a complete surprise that the microglia in the AD brain share some features with ageing microglia given that the condition is strongly associated with age. However, the combined effects of these disorders are less frequently thought about. Furthermore, investigations of neurodegeneration frequently examine "neuroinflammation" and "microglial activation," but these are ill-defined categories that actually comprise a variety of cellular processes. A growing body of research indicates that the development of AD involves substantial connections with immunological processes in the brain as well as the neuronal compartment [13]. Misfolded and clumped proteins interact with pattern recognition receptors on microglia and astrocytes, resulting in the release of inflammatory mediators that aid in the progression and severity of the disease. Several genes that raise the risk of sporadic Alzheimer's disease may also encode proteins that control the inflammatory response and glial clearance of misfolded proteins, according to a genome-wide investigation [14]. External variables, such as systemic inflammation and obesity, are likely to obstruct the brain's immune functions and accelerate the development of disease. Future therapeutic or preventive approaches for Alzheimer's disease might result from targeting these immune pathways and modifying risk factors. AD is a progressive neurological condition that develops with age and causes dementia by impairing memory and cognitive function [15]. Neurofibrillary tangles, substantial local inflammatory response activation, and amyloid plaque formation are all signs of AD in the brain [16].

NF-kappaB Signaling pathways in Neurological Inflammation

NF-kB is a short name of Nuclear Factor kappa-light-chain-enhancer of activated B cells. It is not a single protein, but a small family of inducible transcription factors that play an important role in almost all mammalian cells. It control DNA transcription, cytokine production, cell survival and other important cell events, especially play a key role in regulating the immune response to infection. There is a lot of evidence to back up the claim that nuclear factor kappa B (NF-κB) signalling affects not only immunity but also inflammation, cancer, and nervous system health. The number of studies on NF-κB activity in mitochondrial function, however, is substantially less and dispersed across the literature. For instance, NF-κB subunits were discovered in the mitochondria in 2001, including IkBα and NF-κB p65 subunits as well as NF-κB pathway proteins like IKKα, IKKβ, and IKKγ, but no follow-up research has been conducted to date. Further consideration reveals that, considering the significance and evolutionary history of both NF-B and the mitochondrion, there are surprisingly little research on the role of NF-κB activity in mitochondrial function [17]. Sen and Baltimore identified nuclear factor-kB (NF-kB) as a transcription factor in B cells in 1986. Rel subfamily members p65 = RelA, c-Rel, and RelB, which contain C-terminal transactivation domains (TADs), and the NF-kB subfamily's NF-kB1 (p50 and its predecessor p105) and NF-kB2 (p52 and its precursor p100) members make up the homo- or heterodimers that make up NF-kB. In 1990, Herzenberg and associates described how TNF-a and phorbol 12-myristate 13-acetate activate NF-kB through intracellular thiols, demonstrating that NF-kB is redox-regulated (PMA). TNF-a-induced NF-kB activation was boosted by lowering glutathione levels (GSH, g-glutamyl-cysteinyl-glycine), the main redox buffer in cells, while NF-kB activation was inhibited by employing N-acetyl-L-cysteine (NAC), the precursor of glutathione production [18]. The NF- kB (nuclear factor -light-chain-enhancer of activated B cells) transcription factor family functions as a pleiotropic regulator of numerous cellular signaling pathways, giving cells a method to react to a number of stimuli linked to inflammation. Both the canonical and non-canonical NF-B pathways will regulate the excited cells. IB-degradation causes the release of NF- kB, which in turn causes the nuclear translocated-heterodimer (or homodimer) to bind to the promoter's kB sites and control the transcription of the genes. Neurons universally express NF- kB, and constitutive NF- kB activation is linked to the processing of neuronal information [19]. The neuronal activity can be modulated by NF-kB via controlling the transcription of genes for chemokines, cytokines, proinflammatory enzymes, adhesion molecules, proinflammatory transcription factors, and other substances. In addition to neurons, glial cells and cerebral blood vessels are also rich in NF-kB transcription factors, and NF-many kB tasks include controlling the inflammatory response in the vicinity of neurons. The brain has a large number of NF- kB transcription factors, which serve a variety of purposes. NF- kB activation by inflammatory mediators has been associated to a number of central nervous system (CNS) illnesses. On neuronal survival, RelA and c-Rel expression have opposing effects. It's significant to note that c-Rel expression in the CNS is essential for anti-apoptosis and lowers age-related behaviors [20]. Additionally, the various NF- kB dimer formation subunits can control neuronal toxicity, neuronal protection, or neuroinflam-

mation. The various NF- kB functions are dependent on the NF- kB dimerization subunits, allowing us to create a novel therapeutic strategy for neuroinflammation [21].

Microglia in neurodegeneration

The immune sentinels known as microglia are a specialized population of macrophage-like cells in the central nervous system (CNS) that are capable of coordinating a robust inflammatory response. Microglia significantly contributes to neurodegenerative and neuroinflammatory diseases. While their harmful interactions with neurons via creation of reactive oxygen species (ROS) and Inducible nitric oxide synthase (iNOS) play a vital part in neurodegeneration, their interactions with Thymus (T) cells are a significant factor in the development of brain autoimmunity [22]. The origin of microglia, their relationship to peripheral monocytes, and their role in disease pathogenesis have all been clarified by novel genetic methods and animal models [23]. Understanding microglia's role in the context of individual disorders will be crucial to develop novel microglia-targeted treatments for CNS diseases because they may have both positive and harmful activities in the CNS [24]. Highly active cells called microglia interact with both neuronal and non-neuronal cells. Pathogen-associated molecular pattern (PAMP) receptors, also referred to as Toll-like receptors, are a significant class of receptors that are expressed by microglia [25]. TLRs 1 through 10 have been discovered in humans to date. Lipoteichoic acid (LTA) (TLR2), double-stranded RNA (TLR3), lipopolysaccharide (LPS; TLR4), flagellin (TLR5), single-stranded RNA (TLR7), and unmethylated CpG DNA (TLR9) are examples of PAMPs that can be detected and responded to by microglia since they express TLR1 through TLR9 [26]. Pathogen-associated molecular pattern (PAMP) receptors, also referred to as Toll-like receptors, are a significant class of receptors that are expressed by microglia. TLRs 1 through 10 have been discovered in humans to date [27]. Microglia may recognise and react to a wide variety of PAMPs, including double-stranded RNA, lipopolysaccharide, lipoteichoic acid (LTA), and TLR1 to TLR9. Microglia patrols the brain parenchyma by continuously extending and retracting their processes [28]. They are also able to change their morphology from ramified to amoeboid, which is a characteristic linked with cell activity. Due to the large variety of receptors they express, microglia can react to pleiotropic stimuli such as plasma proteins, cytokines, and neurotransmitters. They have significant effects on synaptic plasticity and adult neurogenesis and play a key role in the healthy brain as regulators of synaptic functioning and phagocytosis of developing neurons [29]. Multiple foci of increasing necrosis and microglia nodules are signs of T. gondii damage to the central nervous system (CNS) due to vascular involvement by the lesions; necrosis is the disease's most noticeable feature [30]. The principal functions of microglia, which are myelomonocytic innate immune cells in all mammalian organs, are to ward off and phagocytize viruses, bacteria, and other external invaders, as well as to clear away cell debris to aid in wound healing. In the skin, lung, and liver, innate immune cells are sporadic [31]. Microglia, on the other hand, covers every area of the CNS in a pattern resembling tiles. It is clear that microglial cells have functions that are unique to the brain because they make up the complete adult mammalian brain [32]. Monocytes produced from bone marrow were once assumed to be the source of microglial cells. It is now known that microglia arise from a distinct stem cell in the yolk sac, despite the fact that they share many traits with blood-borne monocytes. During the earliest stages of fetal development, ameboid-shaped microglial progenitors colonize the brain [33]. The CNS overproduces neurons, and developing neurons compete for connections, to make sure that the proper neuronal connections are created during brain development. When a neuron loses a competition, it dies; microglia does not really kill these neurons, but rather remove them when they exhibit malfunction or degeneration [34].

Conclusion

Due to their low activation threshold, activated microglia has been proposed as a sensitive marker of early tissue injury. They are present in a wide range of clinical diseases. Neuroimaging and diagnostic neuropathology can both benefit from this. The development of rod-shaped microglia in the cerebral cortex in "general paralysis of the insane" (neurosyphilis) or subacute sclerosing panencephalitis is a classic example of microglial involvement in CNS diseases. Poliomyelitis and other neuronotropic viral infections also cause neuronophagic microglia to gather around affected neurons to form "microglial nodules." The multinucleated giant cell, which may have microglial origins, is the pathological sign of HIV-1 encephalitis. Microglia is noticeable not just in the centre of amyloid plaques but also on their periphery in Alzheimer's disease. While most experts agree that microglia are produced from bone marrow and are members of the monocyte/macrophage lineage, the origin of ramified microglia has long been a subject of debate. The fact that the number of ramified microglia dramatically increased along with the fall of blood-derived ameboid cells (macrophages) in the CNS during the first postnatal weeks was suggestive for the transformation of ameboid cells into resident ramified microglia. However, morphologically speaking, there were no intermediate forms between these brain macrophages and dormant microglia in the developing brain. Multiple intracellular signaling pathways that are involved in the inflammatory response are activated when microgial receptors are engaged by cognate ligands. In microglia, LPS-induced activation of TLR4 activates nuclear factor (NF- kB), cytokine production (including interferon [IFN-β] and tumour necrosis factor [TNF- alpha]), signal transducer and activator of transcription-1 (STAT-1), the production of reactive oxygen species (ROS), and the production of nitric oxide.

Authors Contributions

AS has written the manuscript, VAS has designed the work and communicated the manuscript, TM has co-supervised the entire work, FA has made the paper according to journal instruction and prepared table and figure, WR has formatted and removed typological error from manuscript.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

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