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NEUROINFLAMMATION IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASE. A RATIONAL FRAME WORK FOR THE SEARCH OF NOVEL THERAPEUTIC APPROACH

Abhishek Marwari, Ashish Kumar Verma*, Salman, Pooja Rani, Mohit kumar, Kamal Jeet, Shalu Chauhan, Ankit Tyagi

Department of Pharmacology, Vivek College of Technical Education, Bijnor, (U.P), 246701.

*Corresponding Author: Ashish Kumar Verma

Department of Pharmacology, Vivek College of Technical Education, Bijnor, (U.P), 246701.

ABSTRACT

Neuroinflammation appears to occur as a consequence of a series of damage signals, including trauma, infection, oxidative agents, redox iron, oligomers of τ and β-amyloid, etc. In this context, our theory of Neuroimmunomodulation focus on the link between neuronal damage and brain inflammatory process, mediated by the progressive activation of astrocytes and microglial cells with the consequent overproduction of proinflammatory agents. Here, we discuss about the role of microglial and astrocytic cells, the principal agents in neuroinflammation process in the development of neurodegenerative diseases.

KEYWORDS: neuroinflammation, Alzheimer disease, microglia, astrocytes, nutraceuticals.
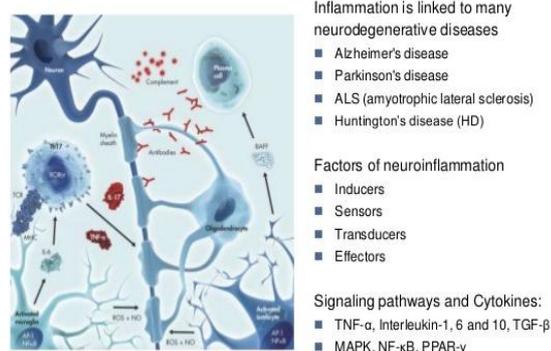
INTRODUCTION

Neurodegenerative diseases (NDDs) are traditionally defined as disorders with selective loss of neurons and distinct involvement of functional systems defining clinical presentation. Comprehensive biochemical, genetic, and molecular pathological examinations have expanded this definition. During the last century, many studies have demonstrated that proteins with altered physicochemical properties are deposited in the human brain in NDDs. Furthermore, not only neurons but glial cells also accumulate these proteins. Involvement of proteins has led to the definition of the concept of conformational diseases.[1] According to this, the structural conformation of a physiological protein changes, which results in an altered function or potentially toxic intra or extra-cellular accumulation. Mutations in the encoding genes are linked to hereditary forms of disease. Molecular pathological, genetic, and biochemical studies have led to reclassification of several disorders, and opened completely new avenues for biomarker development or therapeutic strategies.[2] This review aims to summaries the major developments in this field with an emphasis mainly on sporadic disorders of adulthood. It must be noted that further neurological disorders are associated with neuronal degeneration, including mainly hereditary metabolic diseases and others such as multiple sclerosis or those with immune mediated (autoimmune) etiology; however, these are beyond the scope of the present review.

Neuroinflammation

The inflammatory response is almost always a secondary response caused by an initial event after another, like the response to trauma or infections. However, this means it is a central mech- anism in the neurodegenerative processes. It is this secondary response that will ensue and probably cause a greater loss of neurons over time as compared to the initial injury.[3] Inflammation plays a key role as a driving force that can modulate the development of various neuropathologies. Currently the term "neuroinflammation" is used to describe the inflammatory response originated in the CNS after suffering an injury, where there is an accumulation of glial cells. Particularly astrocytes and microglia responses converge immediately after the injury occurs.

Inflammation in neurodegeneration – neuroinflammation

Inflammation is linked to many neurodegenerative diseases
- Alzheimer's disease
- Parkinson's disease
- ALS (amyotrophic lateral sclerosis)
- Huntington's disease (HD)

Factors of neuroinflammation
- Inducers
- Sensors
- Transducers
- Effectors

Signaling pathways and Cytokines:
- TNF-α, Interleukin-1, 6 and 10, TGF-β
- MAPK, NF-κB, PPAR-γ

A remarkable convergence exists between the mechanisms responsible for the **sensing**, **transduction** and **amplification** of inflammatory responses that result in the production of neurotoxic mediators

In this process, cellular and molecular immune components such as cytokines, complement and pattern-recognition are contributing players, and they can lead to the activation of the glial cells, i.e., microglia and astrocytes. Innate immunity is the first line of defense of the organ- ism against different pathogens. Among the components of the response we can mention pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs), nucleotide-binding, Scavenger receptors (SRs), among others. These receptors recognize not only exogenous pathogen-associated molecular pattern (PAMP) but also endogenous modified molecules called damage- associated molecular pattern (DAMP). Throughout the body, the innate immune system launches inflammatory and regulatory responses via PRRs, phagocytes (macrophages), complement sys- tem, cytokines, and chemokines in order to counteract infection, injury, and maintain tissue homeostasis .Agents involve in innate immunity, are directly related to agents involved in the development of neuroinflammation. Cells of the CNS such as neurons, astrocytes, and microglia along with pattern recognition receptors, cytokines, chemokines, complement, peripheral immune cells, and signal pathways constitute the basis for neuroinflammation.[4] An acute inflammatory response in the CNS is caused by the immediate and early activation of the glial cell in response to noxious stimuli, which is basically a defensive response that leads to repair of the damaged area. But, if the "stimulus" remains persistent in time, an inflammatory condition develops, causing a phenomenon of cumulative damage over time due to the chronic inflammatory reaction.[5] All these events precede and cause neuronal degeneration, generate- ing complex interactions and feedback loops between glial and neuronal cells, leading to cell damage and to the development of a neurodegenerative disease. Thus, neuroinflammation has beneficial or deleterious results in the brain mainly depending on the duration of the inflammatory response. It has been possible to associate a number of neurodegenerative disorders of the CNS to neuroinflammatory events, for example, based on the

appearance of high levels of several pro-inflammatory cytokines: AD, Parkinson's disease,[6] Huntington's disease,[7] multiple sclerosis (MS), amyotrophic lateral sclerosis[8] among others. In all these diseases neuropathological and neuroradiological studies have been performed providing evidence that neuroinflammatory responses could start prior to a loss of neuronal cells. In this regard, increasing evidence has been obtained on the role of certain cytokines in the direct activation of the cellular cascade leading to neurodegeneration and AD. It would be interesting to identify as correlate the neuroinflammation levels that leading to release of these cytokines, which have neurotoxic effects and are involved in the progression of this disorder pathophysiological process.[9] Specifically in AD, it has been demonstrated that there is a high expression of inflammatory mediators in the vicinity of Aβ peptide deposits and neurofibrillary tangles, which in turn are associated with areas of high neurodegeneration;[10] exemplifying the relationship between neuroinflammation and neurodegeneration . Moreover, epidemiological studies have established a link between chronic use of non-steroidal anti-inflammatories (NSAIDs) and reduced risk of AD.[11] These studies reported that the use of long-term NSAID has a protective effect against the development of the disease, delaying the onset of the symptoms or reducing the risk of its occurrence. Although the mechanism behind this phenomenon is still unknown, some hypotheses are inclined to the effects of these anti-inflammatory on the regulation of COX-1 and COX-2 protein, whose levels are elevated in individuals with AD.[14] It has also been observed that the regulation and blockade of the COX-1 in microglia, by effect of NSAIDs induced an improvement in the symptomatology of AD.[12] Results in transgenic animal models of AD, show that NSAIDs reduce in a dose-dependent manner behavioral deficits and the population of activated microglia.[12] Comparative analyses performed in the brains of cognitively normal patients chronically using NSAIDs over age versus those not using NSAIDs revealed no changes in the appearance of senile plaques, but there was a 3-folddecreaseinthenumberofactivated microglia in the brains of chronic users of NSAIDs.[13] AD patients who used NSAIDs compared with another group of patients who did not use NSAIDs, showed a significantly slower progression of disease.[13] These findings suggest that he protect ion provided by the chronic use of NSAIDs.

In patients with AD may partly be derived from the attenuation of microglial activation. Lim et al. have conducted studies of cerebral amyloidosis in transgenic mouse models, and gave evidence of ibuprofen effect on amyloid plaque deposition.[15] After 6 months of treatment with ibuprofen, amyloid plaque deposits were reduced significantly in 10 months old Tg2576 transgenic mice. Also there was a reduction in markers of astroglial and microglial activation.[15] Moreover, in double transgenic animals ibuprofen reduced microglial

activation and decreased the number of amyloid deposits.[16,17] In addition, Choi et al. demonstrated that the treatment of 20-month-old triple transgenic AD (3 X Tg-AD) mice with the COX-1 inhibitor SC-560, significantly improved memory deficits and reduced amyloid deposition and τ phosphorylation in the hippocampus.[18] An explanation is that the mice SC-560 treatment alters the phenotype of activated microglia, reducing the expression of pro- inflammatory factors. Authors postulated that this changes in microglial cells may play a role in the reduction of amyloid charge and τ pathology and in rescuing impaired memory in aged 3 X Tg-AD. As stated above, there is important evidence that early treatment in transgenic animals with NSAIDs may reduce neuroinflammation and Aβ peptide deposition in the brain P.[19] In spite of that it cannot be over- looked that not all results have been favorable, for example, in transgenic mice models of AD, COX-2 selective inhibitors failed to reduce the inflammatory reaction and showed an increase in the appearance of Aβ42 peptide.[20]

Recent findings suggest that alterations in microglia and the production of cytokines and chemokines may be a nearly feature that precedes Aβ deposition in a mouse model of AD.[21] This early microglial activation may well play a role in the appearance of vulnerable neuronal populations, similarly to the situation in AD. On the other hand, clinical trials on the effects of NSAIDs treatments of cognitive decline in Alzheimer's disease patients did not provide clear-cut results, data varied depending on the cognitive test used. For example, results of trials with Naproxen indicate that this NSAID attenuate cognitive decline, but accelerated cognitive decline in fast decliner patients. Conversely, Celecoxib (another NSAID) appears to have similar effects, but attenuated changes in fast decliners.[22] Thus, it is premature to make clinical recommendations, but the findings to date, open several potential avenues of research, and possibly the clinical trials should be replicated in one or more large observational studies. In this context, we can conclude that some NSAIDs are able to reduce the inflammatory response caused by microglial and astroglial cells, but some others are not as effective or may even produce opposite results. This suggests that microglia have different responses after exposure to different types of NSAIDs according to specific mechanism of action of the molecule and also to the source of the primary insult that induces the onset of an inflammatory response. It is also plausible that the response may vary during the course of a given therapy.[23]

Astrocytes
Astrocytes are the most abundant glial cells of the nervous system and constitute about 25% of the cerebral volume.[24] They have multitude of functions:
(i) Inducing the formation of neuronal synapses and influencing their development (synaptogenesis);
(ii) Formation and maintenance of blood- brain barrier;
(iii) Neurotransmission;
(iv) Metabolic regulation;
(v) Ion balance maintenance, and finally
(vi) As a component of the "tripartite synapse" model of neurotransmission, in this model of neurotransmission, synapse consists of three functional elements: pre-and postsynaptic neurons and surrounding astrocytes.

Then in addition to communication between neurons, there is a bidirectional communication between neurons and astrocytes, implying a predominant role of glial cells in the physiology of the nervous system.[25,26] Astrocytes play a key role in the development of the nervous system, since the growing of axons is guided to the target by molecules derived from astrocytes, such as tenascin C and proteoglycans.[27]

Astrocytes are actively involved in synaptogenesis, not only during development but also after CNS injury. In 1997, studies conducted by Pfrieger observed that retinal ganglion cells synap- tic activity was 100 times major in the presence of astrocytes.[28] This increase in synaptic activity mediated by astrocytes is precisely due to the increased number of synapses, which is seven times higher in retinal ganglion cells cultured with astrocytes in the absence of astrocytes.[29] This increase in the number of synapses is mediated by a matrix-associated protein named thrombospondin,[30,31] which belong to a family of five homologous proteins, and at least four of them are expressed in these cell types during development and after brain damage, inducing synaptogenesis. These proteins induce ultra-structurally normal synapse formation, both presy- naptic and postsynaptic.[32]

On the other hand, the metabolic support given by astrocytes, provides active neurons with metabolic substrates through a glucose-lactate shuttle. Increased neuronal activity leads to an increase in glutamate release, which in turn activates astroglial Na+-dependent glutamate transporters, thus increasing cytosolic Na+ concentration in astrocytes. In turn, increased Na+ stimulates glycolysis and lactate synthesis. The lactate is subsequently transported to neurons through specific transporters.[33] The astrocytes are involved in the maintenance of home- ostasis of brain neurotransmitters, being of particular importance for homeostasis and turnover of glutamate by being the main sink of glutamate in the brain. From the bulk of glutamate released during synaptic transmission, several studies have shown that only a minimum percentage of glutamate (~20%) accumulates in the neurons, while the largest amount of this neurotransmitter is absorbed by perisynaptic astrocytes. This process of eliminating extracellular glutamate by astrocytes, it is extremely critical to prevent excite toxicity.[24] Numerous records show that astroglial cells possess highly important functions within the brain. However, pathological modifications of astrocytes have been associated with

several neurodegenerative disorders. These include ALS, MS, AD, Parkinson's disease, Alexander's disease, epilepsy and Rett syndrome.[35] Pathological astrocytes observed in the brains of patients with dementia were initially analyzed by Alo is Alzheimer, which found abundant glial cells in the neuritic plaques. Sub-sequent studies have confirmed that this is a morphological characteristic of reactive astrogliosis in AD that can be found both in brain tissue of patients with AD, and transgenic animal models.[34] In studies of post mortem brain tissue from patients with AD a generalized astrogliosis—manifested by cell hypertrophy and an increase in the expression of Glial fibrillary acidic protein (GFAP) in astroglial S100B protein—can be found.[34] A more detailed analysis of astrogliosis in brains obtained from elderly patients (with and without AD confirmed) has shown a correlation between the degree of astroglios is and cognitive impairment. However, adirect relation between changes in astrocytes and increase in senile plaques has been found (Simpson et al., 2010). Morphological data show that reactive astrocytes associate with some Aβ plaques, but not with all of them, while astrogliosis can also been found in areas without Aβ deposits. This may result from the fact that astrocytes may also respond to other pathological factors in the ageing brain.[36] In the meantime, no significant difference was found in the expression of GFAP in brain tissue samples from patients with and without dementia.[37] Furthermore, it has been shown that fragments of Aβ promote marked inflammatory response in the brain, causing the synthesis of different cytokines and proinflammatory mediators.[38] Within this inflammatory response, astrocytes express a repertoire of receptors for inflammatory cytokines (IL-1β and TNFα), chemokines and damage signals (including TLR ligands),[39] while other receptors and other mediators of inflammation, may be induced after appropriate activation signals from other brain cells.[40] Studies conducted by Van Kralingen, found that a number of inflammatory cytokines were elevated in the CNS following injury. In turn, in various neurological conditions there are elevated levels of specific cytokines (in serum or CSF), correlating with poor results in neurological evaluations. These include TNFα and IL-1β, which have proven to affect the function of the blood-brain barrier. A secondary inflammatory response to IL-1β and TNFα, leads to astrocyte activation, being the long-term effect of these cytokines detrimental to the survival of astrocytes. This reveals a potential new target cell, which may help explain some of the negative effects of these cytokines on brain tissue during neuroinflammation.[41]

Microglialcell

Microglia are widely distributed throughout the brain and spinal cord.[42] These cells can be found in brain, spinal cord, retina and optic nerve, but mainly in the hippocampus and substantia nigra,[43] and correspond to approximately 5–20% of the total population of glial cells in the CNS.[44] These cells are considered as a representative of the immune system in the CNS, since they possess the ability to perform phagocytosis, release cytotoxic factors and behave as antigen presenting cells.[45]

Microglia plays a key role in embryonic development as they can secrete growth factors important for the formation of the CNS, and also contribute to the maturation, regeneration and neuronal plasticity. Furthermore, in their resting form they also are involved in other functions such as neurogenesis, neuroprotection and synaptic pruning, which has been found to be complement dependent.[46] Moreover, these cells are also involved in a number of key processes for them an intenance of homeostasis of brain micro environment, showing various functions. For example, microglia act as activated macrophages and they respond to any type of tissue injury.[46] Thus, the suitable and appropriate function of microglial cells is essential for the homeostasis of the CNS in both diseased and in normal health frame.[48]

Microglia under physiological conditions are usually found in an inactivated state (or resting state) which is characterized by a ramified morphology, small and low expression of macrophage related molecules. When activated, drastic changes in morphology of microglia occurs. Activated microglia are not defined by a particular morphology, but are characterized by having few branchings, and a larger cell body with ameboidal form.[49]

Numerous signals represent a threat to the homeostasis of the CNS, including structures and/or residues from bacteria, viruses and fungi. Abnormal endogenous proteins, complement factors, antibodies, cytokines and chemokines, among others, are also sensed by the microglia elements and subsequently induce activation.[50] Thus, there are two main functional aspects of microglial cells: immune defense and maintenance of CNS homeostasis.

Activation of microglia by TLRs and NOD-like receptors (NLRs) is considered to be "classical" form of microglial activation where innate immune responses include production of proinflammatory cytokines like TNF-α, IL-1 and IL-6, and chemokines. Classical activation also leads to adaptive immune response by expressing major histocompatibility class II (MHCII) molecules and interaction with T cells.[51] Under inflammatory conditions, there is an increase in active immune response and microglia should moderate the potential damage to the supporting tissues, repair and remodeling of the CNS[52] In this state the cells regulate the expression of different surface markers, such as MHCII, growth factors,[53] PPRs, produce more pro-inflammatory cytokines, such as IL–1β, IL-6, IL-12, interferon gamma (INF-γ) and TNF-α.[54] Moreover, activated microglia increase their proliferation[55] synthesize and release cytotoxic factors such as

superoxide radicals (O− 2), nitric oxide (NO) and reactive oxygen species (ROS).[56] Therefore ,it becomes clear that microglials cell have an important role in innate immunity and are them a insource of pro-inflammatory factors in brain. Microglial activation is a phenotypically and functionally different process, since depending on the type, intensity and context of the stimulus; microglial response has a potential neuroprotective or pro-inflammatory effect.[57] It is precisely this delicate balance between the neurotoxic and neuroprotective and between pro-inflammatory and anti- inflammatory which determines the role of microglia in a dis- ease or condition. So based on the current research, microglial activation should not be considered as an all or nothing event or single process, and we must realize that the answers to the pathological events depends on context and adapt as changes in the microenvironment occurs.

RESULT AND DICUSSION

Today, as a result of the lack of effectiveness of current treatments for neurodegenerative diseases, a lot of effort has been invested to enhance the search for new therapeutic targets. Based on the results obtained in patients taking anti-inflammatory drugs, a new possibility has been opened studying the association of inflammatory processes and neurodegenerative diseases pathophysiology.

An important strategy to prevent brain impairment is based on dietary changes and nutritional supplements, functional foods and nutraceuticals. In this regard, there is interesting information coming from studies with the antioxidant and antiinflammatory Andean Compound (called initially as Andean Shilajit). Andean Compound is a very complex mixture of humid substances generated by natural millenary decomposition of vegetal material and is originated as an endemic natural product from the Andes Mountains. Andean Compound and its major active principle fulvic acid emerge as novel nutraceutical with potential uses against neurodegenerative brain disorders.[58,59] Another compound of natural origin, which is currently under study, is curcumin. Curcumin is a natural phenolic compound derived from the perennial herb Curcuma longa (turmeric), and is well known to exhibit anti-inflammatory and antioxidant activities.[60]

CONCLUSION

Based on the results of studies on long-term exposure to anti- inflammatory agents, that show that these drugs are associated with a decreased risk of developing AD, a new interesting therapy may be available.

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