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THE ROLE OF NEUROINFLAMMATION IN THE PROGRESSIVE OF ALZHEIMER'S DISEASES

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ABSTRACT

The idea that neuroinflammation is linked to the pathophysiology of Alzheimer's disease (AD) has been bolstered by a substantial body of information gathered over the last ten years. The classic and alternative pathways of the complement system, pentraxin acute-phase proteins, brain cells including microglia and astrocytes, and other inflammatory elements linked to AD neuroinflammation Peroxisomal proliferators-activated receptors (PPARs), nicotinic acetylcholine receptors (AChRs) of the neuronal type, and cytokines and chemokines. One of the primary pathologic characteristics of AD is beta-amyloid protein (A), which is produced by both astrocytes and microglia. It has been demonstrated that A itself functions as a pro-inflammatory agent, activating a number of inflammatory components. Studies have provided more evidence that neuroinflammation plays a part in AD.

KEYWORDS: Alzheimer’s diseases**,** Pentraxins, Cytokines, Prostaglandin, **Microglia,** Astrocytes, NSAIDs, Glucocorticoid steroid, Neurones.

INTRODUCTION

Neuroinflammation has historically been linked to the kinds of cellular responses seen in persistent infections including tabes dorsalis, TB ofeither the polio virus or the central nervous system (CNS) (Haymaker and Adams, 1982). Leukocytes, particularly T cells, and monocytes infiltrate the central nervous system. This traditional understanding of what neuroinflammation is has been significantly reexamined in light of research on Alzheimer's disease (AD). There is minimal indication of an adaptive immune response, and AD lesions are sterile. However, a large range of chemicals that have been identified as inflammatory

mediators by conventional immunological research are expressed in the lesions. These locally produced chemicals are derived from the host's natural defenses. Naturally, these CNS defenses are also seen in reaction to a viral assault, but because of the significant peripheral immune response, these have been disregarded. Damage to host tissue may arise from an excessively aggressive host response, whether it be systemic or local. According to the traditional theory, this kind of misdirection must result from an autoimmune reaction in which rogue T-cell lines or antibodies are cloned against host proteins (Patrick L et.al, 2002).There is currently accumulating evidence that immunological responses play a significant role in neurode generation, especially as immune-related genetic abnormalities have been proposed to be causes of neurode generation risk factors. There is strong evidence to support the development of therapeutic approaches that control neuroinflammation in order to avoid CNS diseases, as more and more underlying molecular pathways become known. The link between neuroinflammation and the pathophysiology of neurodegenerative illnesses, the key inflammatory signaling pathways implicated in neurodegeneration, and the treatment approaches that target these signaling pathways are the primary topics of this review (Zhang et.al, 2023).

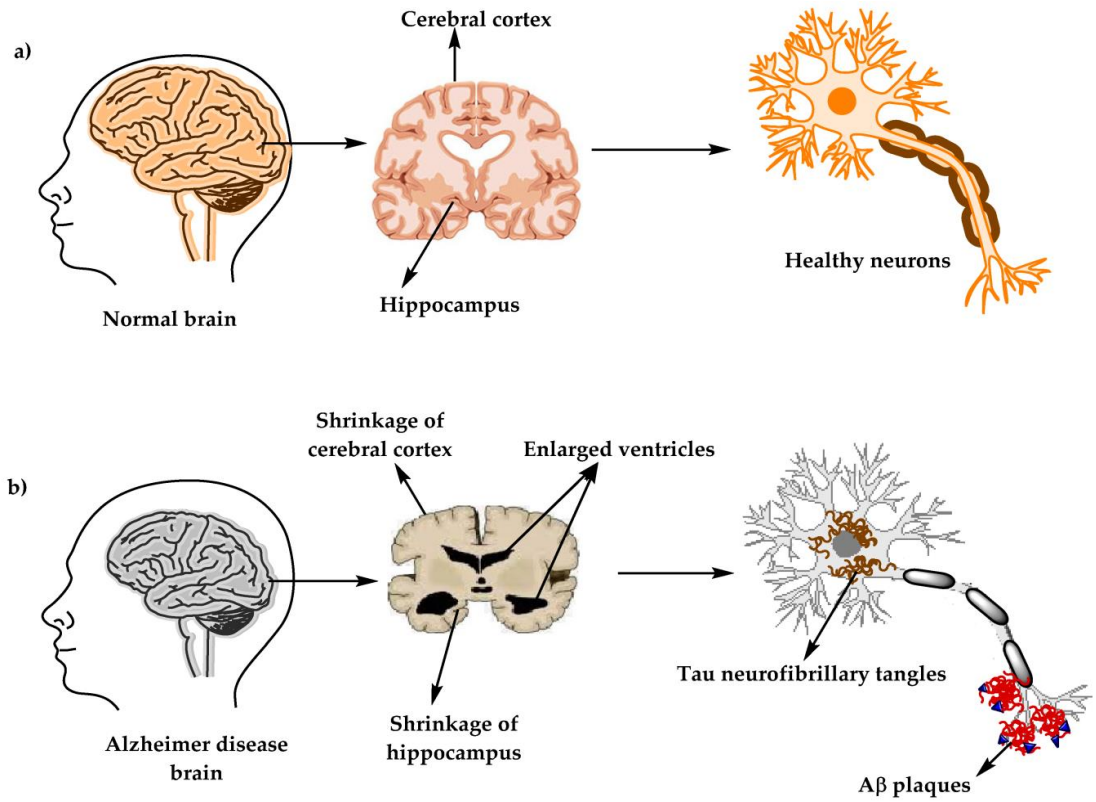

Fig-01 1. The physiological structure of the brain and neurons in (a) healthy brain and (b) Alzheimer's disease (AD) brain.

The mechanism of neuroinflammation and how Alzheimer's disease is related to it

Astrocytes are a crucial type of neurosupportive cell, but microglia serve as the brain's initial line of defense against the immune system. In fact, astrocytes regulate blood flow, oxidative stress, pH, and ion homeostasis to carefully manage the environment. 25, 26 These cells make up the neurovascular unit, which is in charge of the BBB's appropriate operation along with microglia, oligodendrocytes, neurons, pericytes, and endothelial cells. 27 Furthermore, astrocytes play a significant role in synaptogenesis, dynamically modify signal transmission and information processing, control synaptic and neural plasticity, and sustain neurons' trophic and metabolic needs.It is generally known that the neuroinflammatory pathophysiology is more intricate and driven by the activation of various brain cells, even while Aβ deposits alone can trigger an inflammatory response that eventually results in the development of AD. Specifically, mounting data indicates that glial cells, which react swiftly to brain damage and initiate a number of repair processes to restore brain physiology, are primarily responsible for this phenomena. The central nervous system's glial cells are not excitable. Many crucial brain activities are carried out by this extremely diverse group of cells (Bronzuoli et al.2016).

Pentraxins

In general, pentraxins are not regarded as mediators of inflammation. Nevertheless, these are old host-defense molecules that might have early antibody-like properties. They activate complement when properly bound. They are thought to have originated about 200,000,000 years ago from an old gene. Due to their peculiar pentameric structure, two molecules—CRP and AP—have been recognized as pentraxins. As acute phase reactants, the pentraxins fit the description. These reactants are substances that, after a general inflammatory response, cause a 25% or greater change in serum levels. Additionally, CRP is generated in the heart, where it rises after myocardial damage, and in the arteries, where atherosclerotic plaques cause a substantial increase in its production. Following a cardiac attack, serum CRP levels predict survival (Lagrand et al., and strokes, and high normal CRP levels in those who appear healthy are linked to much higher chances of developing harmful cardiovascular events in the future(Patrick L et.al, 2002).

Cytokines

A diverse collection of tiny molecules known as cytokines function in both autocrine and paracrine ways. Interleukins (ILs), interferons, tumor necrosis factors (TNFs), growth factors,

colony-stimulating factors, and chemokines are among their many subfamilies. They share a common involvement in inflammatory responses. They usually work together to make it challenging to assign a particular set of in vivo characteristics to a single cytokine. In AD, only a small number of the cytokines have been thoroughly investigated. TNF-α, I6, IL-1β, and IL-1α are the most important ones. The findings that all of these inflammatory cytokines are up-regulated in AD tissue and are significantly linked to AD lesions first raised the prospect that they could contribute to inflammation in the AD brain. Additionally, at least one peripheral inflammatory disease has been connected to each of these SNPs. It follows that people with genetic variants that increase the expression of inflammatory mediators are more susceptible to autotoxic damage at susceptible locations in a variety of illnesses when exposed to an inflammatory stimuli. The extensive use of TNF-α antibodies or receptor blockers, like infliximab and etanercept, in the treatment of rheumatoid arthritis highlights the significance of TNF-α as an inflammatory trigger. Both forms of TNF-α suppression have a positive impact on the radiographic progression of joint destruction and cause a quick improvement in a number of clinical measures of disease activity and patient functional status (Patrick L et.al, 2002).

Prostaglandin

Because they were initially found in the prostate gland, prostaglandins got their name. They are a class of fatty acids that are produced from the precursor arachidonic acid, and the rate-regulating first step of synthesis is catalyzed by cyclooxygenase (COX). The action of phospholipase on lipid membranes produces arachidonic acid itself. Although prostaglandins are generally thought to influence the activity of hormones, their roles are now widely recognized. Inflammatory mediation is one of the most well-known of them. A great deal of therapeutic attention has been paid to this function. Vane's group (Ferreira et al., 1973) pioneered the field with his seminal finding that aspirin's anti-inflammatory properties stemmed from its capacity to suppress prostaglandin formation. This served as the foundation for the creation of a range of COX-inhibiting substances, which are referred to as nonsteroidal anti-inflammatory medicines (NSAIDs) in general. The identification of a second COX enzyme resulted from some of these medicines' inability to prevent renal prostaglandin synthesis. Cyclooxygenase-1 (COX-1) is the new name for the classical enzyme found on chromosome 9, while cyclooxygenase-2 (COX-2) is the new name for the second enzyme found on chromosome 1. Despite the great degree of homology between the two enzymes, their catalytic pockets are different, allowing for the existence of highly

selective inhibitors for each enzyme, although many conventional NSAIDs block both versions. Given that COX-2 is highly inducible while COX-1 is a rather stable enzyme, there may be some role difference (McGeer, 2000).

Other inflammatory mediator

The number of recognized inflammatory mediators that are elevated in AD is constantly growing (see McGeer and McGeer, 1995, 2001; Neuroinflammation Working Group, 2000 for reviews that provide partial tables). Reactive microglia are linked to several mediators. These microglia envelop the insoluble extracellular deposits of ghost tangles and senile plaques. However, the activated astrocytes that surround the injured sites are obviously linked to other mediators. Others are linked to neurons, which create the extracellular material at first but eventually become the targets of an autotoxic onslaught. Apart from the previously mentioned classes of compounds, there are proteases, especially metallotrix proteinases; thrombin and plastin systems, which are components of the coagulation pathways; proteoglycans; cathepsins and cystatins; intercellular adhesion molecules; and astrocytic products like S-100b and α1-antichymotrypsin. Activated microglia are the most prevalent generator of free radicals (Klegeris and McGeer, 2000).

Receptor roles in progressive of Alzheimer's diseases

Cellular components of inflammation- Microglia, astrocytes, and perhaps to a lesser degree, neurons, are believed to be the main participants in the inflammatory process in AD. These cellular components of the brain play numerous vital roles in the homeostasis and function of (Akiyama et al., 2000a,b).

Microglia- In addition to supporting and safeguarding neurons and their roles in the central nervous system, microglia are immune-competent defense cells that coordinate the CNS endogenous immune response. The majority of the microglia are mesodermally derived macrophages (Streit & Kincaid-Colton, 1995), and they can express complement proteins, pro-inflammatory cytokines, chemokines, reactive oxygen species, and major histocompatibility complex type II (MHC II) (Moore & O'Banion, 2002). Microglia can perform both neuroprotective and neurotoxic functions in the brain, depending on the circumstances that activate them. They also possess phagocytic and scavenger qualities (Streit, Walter, & Pennell, 1999). According to Kalaria (1999), microglia are essential for the cellular response to pathogenic lesions such A and neuritic plaques. Microglia can be drawn to and activated by A, which causes them to gather around A's brain deposits. According to

Rogers and Lue (2001), microglia cultivated from both AD and non-demented brains demonstrated a strong chemotaxis to pre-aggregated A deposits. The expression of scavenger receptors by microglia facilitates their adherence to surfaces coated with A fibrils, which results in the release of reactive oxygen species and the immobilization of cells (El Khoury et al., 1996).

Astrocytes- Although their full functional capacity has not yet been fully elucidated, astrocytes are the most prevalent cells in the brain and are thought to play an active role in brain function. They are linked to the brain's skeletal and connective tissue, maintaining the functional integrity of neuronal synapses and influencing and/or directing neuronal activity. When the brain is injured, astrocytes are thought to respond by laying down glial scar tissue as part of the healing process. It is more challenging to determine how astrocytes contribute to the inflammatory process linked to AD. It is well established that SPs in the AD are linked to reactive At the locations of A deposits, astrocytes and astrocytes cluster (Dickson, 1997). Similar to and overlapping with microglia, they have been demonstrated to secrete a variety of pro-inflammatory chemicals, including interleukins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, complement factors, proteases, and protease inhibitors.

Neurons- The neurons themselves have been implicated in the synthesis of inflammatory products and appear to contribute to the inflammatory process of AD. In AD, neurons can express classical route complement protein mRNAs at noticeably higher quantities. according to controls' brains (Shen, Li, McGeer, & McGeer, 1997). Additional research has shown that completion proteins and their mRNAs are expressed neuronally (Akiyama et al., 2000b; Strohmeyer, Shen, & Rogers, 2000; Terai, Walker, McGeer, & McGeer, 1997; Yu, Bradt, & Cooper, 2002). It has been demonstrated that AD neurons have increased expression of the pentraxins, C-reactive protein, and amyloid P.

A possible link between nicotinic acetylcholine receptors and neuroinflammation

In recent years, there has been experimental investigation into the potential link between the CNS and the inflammatory process. The specifics of this association haven't been established yet, but (Wang et al., 2003). The underlying premise is that vagus nerve stimulation reduces the inflammatory response by preventing macrophages from releasing TNF. Because it is regulated by the neurotransmitter acetylcholine (ACh), this physiological process is known as the "cholinergic anti-inflammatory pathway" (Borovikova, Ivanova, Zhang, Yang, & Botchkina, 2000). The inhibition of the ACh-mediated action by the competitive antagonist

bungarotoxin (BTx) implies that one potential receptor subtype might. Arias (2000) and Arias, Kem, Trudell, and Blanton (2002) evaluated the 7 AChR. The experimental data showing that TNF production is inhibited by electrical stimulation of the vagus nerve in wild-type mice but not in That conclusion is highly supported by subunit-knockout mice (Wang et al., 2003). A comparable regulation mechanism may be present with AD-induced neuroinflammation, even though the "cholinergic anti-inflammatory pathway" is primarily linked to the systemic inflammation process. According to this theory, neuronal-type AChRs play a specific part in the neuroinflammatory process. According to functional studies employing hippocampus astrocytes, the expressed nicotinic receptors exhibit physiologically distinct behaviors in addition to having essentially the same binding reactions as the neural-type 7 AChR (Hosli et al., 2000). For example, AChR stimulation causes astrocytes' intracellular Ca2+ ([Ca2+]i) to rise, which triggers the release of Ca2+ from intracellular reserves that are sensitive to caffeine (Sharma & Vijayaraghavan, 2001). The most likely receptor subtype is the 7 AChR as this activation was suppressed by two particular competitive antagonists of the 7 AChR, methyllycaconitine and Btx (reviewed in Arias, 2000; Arias et al., 2002).

Role of anti-inflammatory agents

Research has examined the use of anti-inflammatory medications as a therapy option for AD patients due to the strong evidence that inflammatory processes play a role in the pathophysiology of the disease. The potential benefits of medications like glucocorticoids and nonsteroidal anti-inflammatory medicines (NSAIDs) for AD patients have been investigated.

NSAIDs: The salicylate, propionic acid, acetic acid, fenamate, oxicam, and COX-2 inhibitor classes are all members of the NSAID drug family. They work by blocking the cyclooxygenase (COX) enzyme, which catalyzes the first stage in the conversion of arachidonic acid to a number of eicosanoids, such as throboxanes, leukotrienes, and prostaglandins. They also have analgesic, antipyretic, and anti-inflammatory properties. Eicosanoids have important regulatory roles in immunological and inflammatory responses as well as cell function. There are two known isoenzymes of the COX enzyme, COX-1 and COX-2, both of which are found in the brain but whose roles are unclear. The homeostatic synthesis of prostanoids is carried out by constitutively expressed COX-1.

Glucocorticoid steroid- Considered powerful anti-inflammatory drugs, steroids work by controlling the transcription of various inflammatory molecules, preventing the synthesis of

enzymes that regulate the creation of prostaglandins, and lowering the expression of complement proteins and cytokines that are pro-inflammatory. Therefore, it is unexpected to learn that the epidemiologic evidence supporting the positive effects of glucocorticoid steroid use in the AD brain is either extremely weak. A randomised, placebo-controlled trial to ascertain whether prednisone treatment slowed the rate of cognitive decline in AD patients revealed no difference in cognitive decline between the treated group and the control group, despite the fact that glucocorticoids were demonstrated to inhibit A induction of chemokines and cytokines in the central nervous system (CNS). In fact, it was discovered that AD patients' serum and cerebrospinal fluid had noticeably higher overall levels of the glucocorticoid cortisol than nondemented control patients.

CONCLUSION

There is too much evidence to disregard that neuroinflammation has a role in AD. However, nothing is known about how this neuroinflammation contributes to AD. Does AD cause neuroinflammation as a byproduct? procedure, or is neuroinflammation a direct cause of it? Although clinical trials, particularly with COX-2 inhibitors, have been unsatisfactory, the results of several epidemiologic studies including anti-inflammatory medications indicate that neuroinflammation may be an early factor in the pathogenesis of the disease. The fact that so many different mechanisms—from the complement system to nicotinic receptors—are engaged in the inflammatory process linked to AD and that more have not yet been identified suggests that the illness is caused by several inflammatory mechanisms complicates matters.

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