



Neuroinflammation in Alzheimer's disease and Involvement of Interleukin-1: A Mechanistic View

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ABSTRACT

Ageing is a universal biological fact and a natural process. It begins from the day we are born, or perhaps even before. Of the world's 580 million elderly, 77 million (22% of total) live in India. The increasing life expectancy of Indians, in the last decade, is likely to result in an increase in age-related disorders like Alzheimer's disease and Parkinson's disease. Alzheimer's disease, the most common disorder of geriatric population, is a chronic, progressive, untreatable neurodegenerative disorder characterized by apraxia, aphasia, agnosia and severe cognitive deficits. Several behavioural changes like anxiety, hallucinations, depression and delusions are also experienced. Lot of progress has been made regarding understanding the pathological pathways involved, yet the available therapy only provide symptomatic relief but do not stop progression of disease. Several of key areas have been recognised and out of them inflammation has been regarded as inseparable and crucial factor involved. Interleukin-1 is a key molecule in systemic immune responses in health and disease and has analogous roles in the brain where it contributes to neuronal degeneration by energy dysfunction and triggering production of other cytokines, nitric oxide and others. IL-1 over expression is also associated with rheumatoid arthritis, vascular dementia, diabetes mellitus, periodontitis, systemic sclerosis, autoimmune encephalomyelitis and cerebral infarction. Present review is an effort to present IL-1 as potential therapeutic target in treatment of Alzheimer's disease by linking it with several of pathological factors like amyloid β , neurofibrillary tangles, neuron loss and cholinergic dysfunction.

Keywords: Alzheimer's disease, cytokine, interleukin-1, microglia.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia worldwide ^[1] associated with progressive cognitive and memory loss and characterized by senile plaques and deposition of amyloid beta peptide (A β), neurofibrillary tangles in brain tissue, degeneration of cholinergic pathways, and neuronal degeneration in brain (cerebral cortex and hippocampus). ^[2]

It is estimated that nearly 13-16 million people will suffer from AD by 2050 and, among those, nearly 13% of individuals over age 65 may be affected. ^[3,4] Senile plaques (SPs) and neurofibrillary tangles (NFTs) are common features in AD brain. SPs are extracellular A β deposits derived from amyloid precursor protein (APP) while NFTs are intraneuronal structures composed of tau protein. Clinically AD is characterized by impairment in memory, visuospatial skills, complex cognition, language, emotion and personality. ^[5]

Most AD cases are sporadic, with multiple risk factors, such as aging, environmental stress and diet, suggested to play critical pathogenic roles. ^[5] Still, the exact cause of AD remains elusive, mounting evidence continues to support the involvement of inflammation in the development of AD. ^[6] There are evidences for the convergence of the mechanisms responsible for the sensing, transduction, and amplification of inflammatory processes that result in the production of neurotoxic mediators. ^[7-8] In the AD brain the A β proteins, neurofibrillary tangles and neuronal degeneration seem to be the most likely sources of inflammation. Further, findings of reactive glial cells (i.e., microglia and astrocytes) at sites of amyloid plaques ^[9-10] have suggested that AD is a neuroinflammatory cascade. ^[11-12]

Traditionally thought of as an immunologically privileged organ, now, central nervous system (CNS) is known to have an endogenous immune system that is coordinated by immunocompetent cells such as the microglia. The inflammation associated with the CNS (neuroinflammation) differs from that found in the periphery. The brain lacks pain fibers, making it difficult to recognize the occurrence of inflammation and the classic signs of inflammation such as

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rubor (redness), tumor (swelling), calor (heat), and dolor (pain) are typically not seen in the CNS.^[13]

Inflammation in brain

Inflammatory responses within the brain are mainly carried out by activated microglia and reactive astrocytes. Microglia was first identified as brain phagocytes in 1919.^[14] In the normal brain, they are generally ramified in their resting state. In this stage, microglia does not produce any pro-inflammatory or reactive oxygen/nitrogen molecules. However, following pathological and/or traumatic insults microglia become activated and assumes an amoeboid morphology and increase in size. In addition, certain receptors are upregulated in activated microglia. These activated microglia can be detected by various antibodies and lectins including Mac-1/CD11b, HLA-DR, CD45, RCA-1, and F4/80.^[6] Once activated, microglia phagocytose foreign substances and release pro-inflammatory molecules, such as cytokines that include interleukins (ILs), interferons (INFs), tumor necrosis factors (TNFs), and growth factors that further activate other inflammatory responses and thus potentiate the cycle.^[5]

The production of cytokines is increased in inflammatory states and they function by regulating the intensity and duration of the immune response. They are produced by both microglia and astrocytes in the CNS.^[15] A β has been shown to increase expression of several cytokine mRNAs.^[16] Activated microglia are a major source of ROS in the AD brain, further highlighting the potential molecular mechanism by which microglia inadvertently enhance disease progression.^[6]

The immune network depends on specialized cells in every tissue or organ to provide surveillance for potentially foreign agents, to signal to the rest of the immune system cells their presence and to remove debris. Microglia functions in phagocytosis, recruitment of T cells, and presentation of antigens. At rest these highly ramified cells can surveil up to 50 μ m of extracellular brain tissue with some overlap between microglia through a continuous extension and retraction of processes at speeds up to 1.5 μ m/min. When activated microglia release complement proteins and inflammatory cytokines, such as IL-1 and IL-6, chemokines, reactive oxygen species, nitric oxide, TNF- α and IL-1 β , and matrix metalloproteinases. These released products have been demonstrated to have a direct role in neural damage in co-cultures of activated microglia and neurons as well as in AD mouse models.^[17]

Interleukin-1

Interleukin-1 was first described in 1972 as a lymphocyte-activating factor^[24] and later was shown to exert a variety of effects including induction of inflammation, body temperature increase, proliferation of T and B cells, induction of acute phase proteins and prostaglandins and regulation of hematopoiesis. Its activities are not restricted to the immune system. Interleukin-1 is also involved in the regulation of blood calcium levels, stimulation of proliferation of various cells, regulation of blood pressure or modulation of sleep. However, IL-1 represents one of the most important mediators of the inflammatory response that induces a cascade of proinflammatory effector molecules.^[25]

Interleukin-1 is a term for two distinct but related proteins, interleukin-1 α and interleukin-1 β , encoded by two separate genes. Both of them are produced in consequence of stress or cell injury as 31-kDa precursors which undergo proteolytical

cleavage by specific proteases during the process of maturation. The major interleukin-1 producing cells are macrophages, but many other cells like neutrophils, lymphocytes, dendritic cells, keratinocytes, endothelial cells, hepatocytes, fibroblasts or muscle cells have been shown to synthesize IL-1. Main target cells of IL-1 actions are primarily cells of the immune system such as monocytes, lymphocytes, granulocytes, dendritic cells, but this cytokine can affect many other cells like epithelial cells, fibroblasts, endothelial cells or smooth muscle cells.^[25]

IL-1 α is constitutively expressed by many cell types under physiological conditions and its synthesis is stimulated during inflammation. On the contrary, IL-1 β is not produced unless the cell receives an inflammatory signal and also its cleavage by caspase-1 is a tightly regulated process. Moreover, while mature IL-1 β is released from cells via an ATP-dependent non-classical secretory pathway including P2X7 receptors and pannexin-1,^[26-27] the release of IL-1 α seems to employ a different pathway dependent on copper ions and protein product of the S100A13 gene.^[28]

The 9 genes of the IL-1 family include the 3 well-defined IL-1A, IL-1B, and IL-1RN (receptor antagonist) genes. These have all been mapped to a 430-kb section of DNA on the long arm of human chromosome 2.^[29] Of the gene products, IL-1A and IL-1B are agonists, whereas IL-1Ra is a competitive antagonist for the IL-1 receptor and is therefore a primary negative regulator of the proinflammatory IL-1 response.^[30]

IL-1 has a potent modulatory effect on neurons^[31] and is over expressed in brain of patients with Alzheimer's disease. IL-1 has an important neuromodulatory role in hippocampus^[32] and is a common trigger for age and stress-induced impairments in long-term potentiation.^[33] An interleukin-1-driven cytokine cycle of molecular and cellular events and interactions has been proposed as a basic pathophysiological mechanism underlying the progression of Alzheimer's pathology including conversion of diffuse amyloid deposits into diagnostic neuritic β -amyloid plaques.^[34]

IL-1 manifests properties that include promoting the synthesis and processing of the A β precursor protein, enhancing neuronal acetylcholinesterase activity, microglial activation and expression of further IL-1 production, astrocyte activation, and expression of the cytokine S100B by the astrocytes.^[35-36] S100B is also an inducer of neuronal expression of A β precursor protein^[37-38] and has been shown to be associated with NFTs.^[39]

IL-1 and cholinergic dysfunction

Furthermore, cholinergic dysfunction in Alzheimer's disease has long been recognized^[40-41] and the early memory deficits characteristic of Alzheimer's disease have been attributed, in part, to cholinergic hypofunction, with hyperactivity of acetylcholinesterase (AChE). Influence of IL-1 on AChE makes it an interesting target and recent developments have focused on drugs which inhibit acetylcholinesterase and thus increase the availability of acetylcholine within the brain.^[42]

Acetylcholinesterase hydrolyzes the neurotransmitter acetylcholine at postsynaptic membranes of central cholinergic synapses, thus terminating synaptic transmission.^[43] AChE is a postsynaptic enzyme that terminates cholinergic synaptic transmission through hydrolysis of acetylcholine^[44] and is prominent and over expressed by neurites associated with β -amyloid plaques in Alzheimer brain.^[45] AChE, in turn, has been shown to regulate

processing of the β -amyloid precursor protein (APP) ^[46] and to accelerate assembly of amyloid peptide into β -amyloid fibrils *in vitro*, ^[47] suggesting a link between AChE overexpression and β -amyloid formation. IL-1 released from activated microglia directly induces increases in the acetylcholine-degrading enzyme, acetylcholinesterase, production, and activity in neurons. ^[48]

Overexpression of human AChE in neurons of transgenic mice produces progressive cognitive deterioration as assessed by the Morris water maze, ^[49] suggesting that downregulation of cholinergic function is detrimental to spatial memory. ^[50] AChE may also play a role in cellular development and neuronal growth, unrelated to its classic acetylcholine-hydrolyzing activity. ^[51-52]

Furthermore, AChE also contribute to the amyloid pathology of Alzheimer's disease, because β secretase activity, necessary for generating β amyloid from β APP, is under muscarinic receptor regulation, ^[53] suggesting that declines in cholinergic neurotransmission would favour β amyloid formation and direct physical interactions between AChE and β -amyloid promote formation of amyloid fibrils. ^[47]

IL-1 and energy metabolism

Glucose is the main source of energy for the brain and for most peripheral tissues. Thus, the maintenance of appropriate levels of glucose in blood and tissues is essential for survival and, as known, glucose homeostasis is controlled at central levels. Low, subpyrogenic doses of IL-1 induce a profound, long lasting hypoglycemia that is not related to possible insulin secretagogue effects of the cytokine. ^[54-56] This effect, which is also observed in insulin resistant animals, develops in mice against increased levels of counter regulatory hormones such as catecholamines, glucocorticoids, and glucagon. There is also evidence that the hypoglycemic effect of IL-1 can be triggered at central levels since intracerebroventricular administration of the cytokine induces a reduction in blood glucose levels. ^[57] However, the most surprising effect is observed when mice and rats are challenged with a glucose load several hours after a single intraperitoneal injection of IL-1. ^[58] In this situation, it is clearly seen that, following a transient elevation of glucose levels in blood; its concentration returns to the previously reduced levels and the animals remain hypoglycemic for several hours more. These findings strongly indicate that IL-1 changes the rigid set point that characterizes glucose homeostasis.

IL-1, A β & TAU hyperphosphorylation

Beside this IL-1 is direct toxic to neurons and is responsible for hyperphosphorylation of Tau. Neurofibrillary changes, in the form of neuritic plaques, neuropil threads, and neurofibrillary tangles, are key histological features of AD. Tau is one of the microtubule-associated proteins that stabilizes growing axons necessary for the development and growth of neurites. However, in AD, for unknown reasons, tau becomes excessively phosphorylated and appears in paired helical filaments, dystrophic neurites, and neurofibrillary tangles. ^[59] This neurofibrillary pathology suggests a loss of axonal integrity and an eventual decline in connectivity and synapses, a consistent correlate of dementia in AD. ^[60-61]

Activated microglia increase tau phosphorylation and decrease steady-state levels of synaptophysin through release of IL-1 these IL-1-induced changes occur before significant neuronal cell loss associated with microglial neurotoxicity is

detectable and the effects of IL-1 on tau and synaptophysin are mediated, at least in part, through activation of p38-MAPK. ^[62] Activation of p38-MAPK is involved in neuronal responses to various stresses, ^[63-64] and this kinase is closely related to hyperphosphorylated tau protein in AD. ^[65]

Three possibilities have been proposed on the basis of the neuropathology: (1) loss of synapses is a nonspecific consequence of global neurodegenerative changes that include neuronal loss; ^[66] (2) loss of synapses results from the direct neurotoxicity of amyloid β -peptide (A β) ^[67] and (3) loss of synapses results from cytoskeletal changes caused either actively by tau aggregates or passively by loss of tau function. ^[68-69]

IL-1 promotes neuronal production of β -amyloid precursor protein and its derivatives ^[70] and IL-1-mediated proinflammatory sequel could damage neuronal connectivity via mechanisms beyond neurotoxic effects of A β production. ^[62]

The induction of tau phosphorylation by IL-1 *in vitro* ^[62] and *in vivo* ^[65] indicates that IL-1 might potentially contribute to the reorganization of the cytoskeleton, interrupt normal microtubule assembly and axon stabilization, and eventually result in loss of synaptic proteins and synapses. This is supported by the observations in AD that a loss of synaptophysin is observed in tangle-bearing neurons ^[71] and that activated microglia correlate with neurofibrillary pathology, ^[72] including intracellular tau pathology. ^[73]

The overexpression of IL-1 observed in Alzheimer's disease could potentially contribute directly to the neuronal dysfunction and loss seminal to the disease. With regard to direct toxicity, elevating concentrations of IL-1 *in vitro* are toxic to neuronal explants cultures. ^[74]

The increased tissue levels of IL-1 and the neuronal dysfunction in Alzheimer's disease may be attributable in part to increased production and activity of the IL-1-converting enzyme (ICE), which converts pro-IL-1 α to mature IL-1 α . ICE activity and expression are increased in Alzheimer's disease, and this increase is related to neuronal DNA damage as well as to compromised, neuronal function. ^[75-76] Overexpression of ICE by plaque- and neuron-associated microglia may contribute to neuronal DNA damage associated with neuritic A β plaque progression ^[77] and with neurons bearing neurofibrillary tangles in Alzheimer's disease.

IL-1, a key molecule in systemic immune responses in health and disease, has analogous roles in the brain where it may contribute to neuronal degeneration ^[78] by triggering production of other cytokines and nitric oxide. ^[79] IL-1 over expression is associated within hours after head injury, ^[80] in chronic, intractable epilepsy ^[81] and in AIDS ^[82] each of these conditions has been associated with Alzheimer's disease itself or precocious development of Alzheimer pathology. ^[83-84]

Considerable evidence gained over the past decade has supported the conclusion that neuroinflammation is associated as an integral and inseparable part of pathogenesis of Alzheimer's disease. Present review precisely yet incompletely demonstrates the involvement of IL-1 in the progression of AD. In this review the evidences proves IL-1 to be a good target in finding a cure for Alzheimer's disease treatment as it appears to interact with multiple factors involved in AD progression.

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