Glial Activation and Synaptic Neurotoxicity in Alzheimer’s disease: A Focus on Neuroinflammation

1Shivika Rai, 2Pradeep K. Kamat, 2Chandishwar Nath and 1Rakesh Shukla
1Division of Pharmacology,
2Division of Toxicology, CSIR-Central Drug Research Institute, P.O. Box 173, Lucknow, Uttar Pradesh, 226001, India
3Department of Physiology and Biophysics, University of Louisville, School of Medicine, (KY), 40202, USA

ABSTRACT
Background: Alzheimer’s Disease (AD) is the most common neurodegenerative disorder and extensive evidence of earlier report has supported the conclusion that neuroinflammation is associated with AD pathology. The pathological hallmarks of AD are senile plaques, neurofibrillary tangles and neuronal degeneration. Results: Glial activation is the key factor in neuroinflammation which contributes to neurodegeneration and synaptic abnormalities are one of the leading causes of AD. Inflammatory process in brain also causes excitotoxicity and apoptosis which leads to neuronal cell death. It is inferred from several studies that excitotoxicity; free radicals generation and altered synaptic function encouraged by activated glial cells are associated with AD neurotoxicity. Conclusion: So, collective data suggested that glial activation, which might be a driving force of synaptic-neurotoxicity, considered as a new therapeutic approaches targeting the central nervous system may achieve the essential pharmacological control of AD neurotoxicity. In this review, we consolidate and categorize the glial activation and synaptic neurotoxicity which contribute in neurodegenerative processes during AD pathology.

Key words: Glial activation, neuroinflammation, free radicals, synaptic function, alzheimer's disease


INTRODUCTION
Alzheimer’s Disease (AD) is the most common form of dementia and characterized by severe neurodegenerative changes, such as cerebral atrophy, loss of neurons and synapses (Selkoe, 2001). Neuroinflammation is a pathological hallmark of AD and inflammation clearly occurs in pathologically vulnerable regions of the AD brain (Mrak and Griffin, 2001; Kamat et al., 2012a, b). The Central Nervous System (CNS) has its own resident immune system, in which glial cells (microglia, astrocytes and oligodendrocytes) serve as a supportive and nutritive role for neurons (Singh et al., 2011; Ricci et al., 2009). The evidence inferred a close association of neuroinflammation with the pathogenesis of several degenerative neurologic disorders, including AD (Mrak and Griffin, 2001; Ifuku et al., 2012). Reactive astrocytes can contain substantial amounts of different forms of amyloid beta, including amyloid beta 1-42 (Aβ42) as well as truncated forms (Nagele et al., 2004; Thal and Braak, 2005). Reactive astrocytes can take up and degrade extracellular deposits of Aβ42 (Wyss-Coray et al., 2003) and that this function is attenuated in ApoE-/astrogliocytes (Koistinaho and Koistinaho, 2002), suggesting that reactive astrocytes functions or dysfunctions could play a role in the progression and severity of AD. The intensity of reactive astrogliosis, as determined by Glial Fibrillary Acidic Protein (GFAP) levels, has been reported to increase in parallel with increasing progression of pathological stages in AD (Ricci et al., 2009). These normal glial functions can sometimes result in a more severe and chronic neuroinflammatory cycle that actually promote or propagate neurodegenerative disease (Skaper, 2007). The pathological hallmarks of AD are senile plaques, neurofibrillary tangles and neuronal degeneration. Activated astrocyte and microglia produces a variety of proinflammatory mediators and neurotoxic factors, including cytokines, such as tumor necrosis factor (TNF-α); interleukin-1β (IL-1β); anti-inflammatory cytokine (IL6, IL10, IL4) and free radicals, such as Nitric Oxide (NO) and superoxide (Rock et al., 2004). These free radicals further trigger the neuronal damage via formation of pro-inflammatory agents and associated...
Fig. 1: Flow diagram of graphical abstract depicts the mechanism of glial activation and further effects on synapse dysfunction mediated AD pathology.

cytotoxic products during neuroinflammation can be detrimental to neurons by altering synaptic function (Mattson, 2000) (Fig. 1).

Functional neuroimaging data suggest that pre-symptomatic AD is characterized by changes in synaptic function (William et al., 2012). Neuroinflammation as well as excitotoxicity induced cell death alter the synaptic function in AD which is accompanied by synaptic neurotoxicity. These synaptic changes may contribute to the progressive cognitive decline and behavioural changes associated with AD. Although significant progress has been made over the last few decades in understanding the function of glial cells in the brain, their cellular and functional response to injury during the progression of AD remains largely unexplored (Attwell et al., 2010; Halassa and Haydon, 2010). But still debates are there how glial activation leads to neurotoxicity and affects synaptic function. The design of more rationale therapeutics; for example, rather than suppressing inflammation, coordinating specific elements of the inflammatory machinery may be a more appropriate therapeutic objective.

In this review, we described about the role of glial activation, synaptic neurotoxicity and their implication in AD. We also described the therapeutic approaches targeting glial activation and neuroinflammation as a pathophysiological process contributing to the onset of AD like pathology.

**Astrocytes:** Astrocytes are the most frequent cells in central nervous system which are generally thought to emulate the metabolic activity of neurons and neurotransmitters around synapses (Haydon and Carmignoto, 2006). Several reports suggested that activated microglia promotes astrocytic activation in pathological condition (Verkhatsky and Steinhauer, 2000; Medeiros and LaFerla, 2013). There are various cytokines, among them interleukin-1 (IL-1) is a pivotal mediator, not only because of its fast release in these pathological conditions, but also its ability to upregulate other inflammatory cytokines, such as IL-6 and tumor necrosis factor alpha (TNF-α) (John et al., 2005). IL-1 which has been reported to be mainly produced by microglia is closely associated with various diseases and established cross talk between microglia and astrocytes (Griffin, 2006). Increased IL-1 expression has been detected in reactive microglia surrounding amyloid plaques in AD (Shafel et al., 2007). Astrocytic activation which leads to astroglisis leads to GFAP upregulation (John et al., 2004; Lee et al., 2010). Moreover, IL-1 has been
shown to induce nuclear hypertrophy and intercellular adhesion molecule-1 (ICAM-1) expression in astrocytes (Allbrecht et al., 2002; Kyrkanides et al., 1999). Prostaglandin (PG) D2 also contributes to activation of microglia/astrocytes (Niranjan et al., 2011). Kempuraj et al. (2013) report that GMF (glial maturation factor) induced IL-33 release and that IL-33 augments GMF-induced tumor necrosis factor-alpha (TNF-α) release from mouse astrocytes CCL2, TNF-α and nitric oxide release through phosphorylation of ERK in mouse astrocytes.

**Microglia:** Microglia represent the brain's internal immune system, thus being considered as the first line of defense in the Central Nervous System (CNS) during early development (Ransohoff and Perry 2009). Microglia manage immunosurveillance and mediate inflammation, both suggested being important in AD (Olsson et al., 2012; Cren et al., 2012). In response to injury, microglia contribute to the neuroinflammatory response and undergo rapid morphological and functional activation which includes phagocytosis, antigen presentation, as well as the production and secretion of Reactive Oxygen Species (ROS), cytokines and growth factors (Nimmerjahn et al., 2005; Ransohoff and Perry, 2009; Hanisch et al., 2007). Increasing data demonstrate that microglia may exert either a neurotoxic or neuroprotective effect depending on the physiological conditions. In contrast, alternatively activated microglia block proinflammatory responses and generate high levels of anti-inflammatory cytokines (IL-10, IL-4) and neurotrophic factors (Tiemessen et al., 2007; Gordon and Taylor, 2005). They would be activated immediately if there are abnormal substances, such as cell necrosis factors, proinflammatory cytokines and other foreign particles present inside the cell (Davalos et al., 2005). They also undergo rapid proliferation in order to increase their number for the upcoming battle, demonstrated by upregulation of complement receptor type 3 (OX42) (Kim and de Vellis, 2005). Many signals, such as Major Histocompatibility Complex (MHC) antigens, T- and B-lymphocyte markers and other immune cell antigens, begin to appear on microglia (Wang et al., 2002), which make them as Antigen-presenting Cells (APCs) (Clavariola and Alcocer-Varela, 2004). Microglia migrate to the invaded area (known as chemotaxis), engulf the offending material (phagocytosis) and secrete proinflammatory factors and neurotoxic factors, including cytokines, such as tumor necrosis factor (TNF-α); interleukin-1β (IL-1β); and free radicals, such as Nitric Oxide (NO) and superoxide (Minetti et al., 1998). NO is also produced by activated astrocytes and has also become one of the major contributors in the formation of reactive nitrogen species. Reactive Oxygen Species (ROS) and NO which have been over expressed during the neuroinflammatory process in AD model of rat (Tyagi et al., 2008).

**Neuroinflammation:** Neuroinflammation is the natural response of the immune system to injury or infection in the Central Nervous System (CNS). The neuroinflammatory processes is initiated via activation of macrophages in the periphery and microglia and/or astrocytes in CNS which leads to the release of proinflammatory mediators, such as cytokines (Duffield, 2003). The inflammatory response is essential in maintaining homeostasis, but has the potential to cause deleterious effects if not tightly controlled (Hanisch et al., 2007). Overproduction of proinflammatory cytokines and excessive inflammation is characteristic of many neurodegenerative diseases (Blasko et al., 2004; Whitton, 2007) and can lead to systemic shock and sepsis. Anti-inflammatory mediators, such as the cytokines interleukin-10 (IL-10) and interleukin-4 (IL-4), transforming growth factor b (TGF b) and interleukin-1 (IL-1) receptor antagonists and the sympathetic nervous system, serve to regulate the inflammatory response (Pavlov et al., 2003).

**Acute and chronic neuroinflammation:** Acute neuroinflammation triggers activation of resident microglia and the release of inflammatory mediators such as cytokines and chemokines (Tansey et al., 2007). Acute inflammation is typically short-lived and unlikely to be harmful to long term neuronal survival. It is believed that an acute neuroinflammatory response is generally beneficial to the CNS, since it tends to minimize further injury and contributes to repair of damaged tissue. On the other hand chronic inflammation produces long lasting and self-perpetuating neuroinflammatory mediators that remain after the initial neuroinflammatory insult. Proinflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), IL-6 and chemokines including interferon gamma, macrophage inflammatory protein and Inducible Protein (IP)-10 are released by activated microglia that promotes neuroinflammatory process. Proinflammatory cytokine regulate expression of many genes, including gene transcription for Arachidonic Acid (AA) cascade enzymes in various cell types via nuclear kappa B (NF-κB) or AP-2 (Acarin et al., 2002). In the brain, AA and its metabolites influence signal transduction, gene transcription, neuronal activity, apoptosis and other processes (Ram and ScC, 2000).

**Glia cells and Alzheimer's disease:** Glial cells (astrocytes, oligodendrocytes and microglia) are
significantly abundant in the brain; and pathologically they linked to AD. Large numbers of available data imply that Aβ plays a role in inducing many of the alterations in glial cells (McGeer and McGeer, 2002). Microglia play important roles in responses of the brain to injury and infection and activated microglia congregate around amyloid plaques and degenerating neurons and may produce toxins and inflammatory cytokines that contribute to the neurodegenerative process in AD (McGeer and McGeer, 2002). The severe changes in glial cells in AD may promote neuronal degeneration as well as may also remove Aβ, a potentially beneficial action of these immune cells (Jantzen et al., 2002). In addition, although synapses degenerate in vulnerable neuronal circuits, the remaining synapses may increase in size to compensate and astocytes may play a role in this process (Murai et al., 2003). Moreover, the production of neurotrophic factors such as basic fibroblast growth may increase in astocytes associated with Aβ deposits (Cummings et al., 1993) and these neurotrophic factors as well as certain cytokines (Barger et al., 1995) may stabilize the neurodegenerative process in AD.

What does glial activation? Glial cell activation in the central nervous system (CNS) leading to an inflammatory reaction in the brain plays a central role in the development and progression of AD (Meda et al., 2001). Activated microglia and astrocyte lead to formation of proinflammatory cytokines and leads to synaptic dysfunction, which is an important pathophysiological component of AD (Bell and Claudio, 2006). Microglial activation leads to the generation of free radical Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS) that triggers the neuronal damage (Liu et al., 2003). The activation of microglia releases proinflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-beta (IL-1β) (Merrill and Benveniste, 1996). Tanaka et al. (2006) suggested that pro inflammatory cytokines, oxygen and nitrogen centered free radicals contribute to the neurodegenerative processes. Proinflammatory cytokines like TNF-α and IL-1β are suggested as important mediator in brain pathology of AD (Tan et al., 2007; Rai et al., 2013; Kettenmann and Verkhratsky, 2008). Neuron can activate glia via various neurotransmitters or modulators, such as glutamate, Nitric Oxide (NO) and others (Liu et al., 2004a, b; Verge et al., 2004). This phenomenon is accompanied by death of neuronal cells and may be connected with inflammatory events arising from the production of a wide range of cytokines and chemokines (Struzynska et al., 2007).

Glial activation, Aβ accumulation and kinases: Pro-inflammatory stimuli, including cytokines like Interleukin-1β, Interleukin-6 and Interferon-α, in the brain have been proposed to exacerbate existing AD neuropathology by increasing amyloidogenic processing of APP and promoting further Aβ accumulation. Aβ-induced astrocyte activation and to exert a marked protective effect on neurons and inflammatory process is a consequence of the over-activation of glial cells (Scuderi and Steardo, 2013). Aβ42 induces ERK activation and glial cell proliferation independently of apoptotic processes and suggested that inhibiting the EGFR/ERK pathway and glial cell proliferation and by suppressing the JNK pathway and apoptosis (Park et al., 2013). On the other hand, anti-inflammatory cytokines have been suggested to be neuroprotective by reducing neuroinflammation and clearing Aβ (Chakrabarty et al., 2012). Bradykinin (B1 Receptor) B1R activation also plays an important role in the regulation of activated glial cell accumulation and release of pro-inflammatory mediators. Therefore, the modulation of the receptor may represent a novel therapeutic approach for AD (Passos et al., 2013). APP/PS1 mice exhibited improved cognitive and synaptic function, reduced glial activation and lower amyloid levels after treatment with AAV-Gh2 vectors drove the expression of VIVIT, a peptide that interferes with the immune/inflammatory calcineurin/NFAT (nuclear factor of activated T-cells) signaling pathway. Activated astocytes in AD and lay the groundwork for exploration of other novel astrocyte-based therapies (Furman et al., 2012). Cameron et al. (2012) reported that microglial IRAK4 is necessary in vitro for Aβ to activate the canonical pro-inflammatory signaling pathways leading to activation of p38, JNK and ERK MAP kinases and to generate reactive oxygen species. IRAK4 activation acts normally to regulate microglial activation status and influence amyloid homeostasis in the brain. The up-regulation of GMF in astocytes leads to the destruction of neurons suggesting a novel pathway of GMF-mediated cytotoxicity of brain cells and implicated its involvement in the pathogenesis of inflammatory neurodegenerative diseases. The increase in GMF and cytokine/chemokine expression was correlated with reactive glial fibrillary acidic protein positive astrocytes and ionized calcium binding adaptor molecule 1 (Iba-1)-positive microglia in 3×Tg-AD mice (Zaheer et al., 2013). The deposition of Aβ in brain areas involved in cognitive functions is assumed to initiate a pathological cascade that results in inflammation, synaptic dysfunction, synaptic loss and neuronal death (Fig. 2)(Walsh and Selkoe, 2004).

Cytokine receptor: The cytokine tumor necrosis factor-alpha (TNF) plays a critical role in coordinating and maintaining immune/inflammatory responses both
inside and outside the brain. TNF binds to two distinct membrane receptor subtypes, TNFR1 and TNFR2, which are, in turn, coupled to distinct intracellular signaling cascades (McCoy and Tansey, 2008). Aging and several neurodegenerative diseases are associated with elevated brain levels of TNF (Gavilan et al., 2007). In animal models of disease, TNF appears to be a key contributor to chronic glial activation and impaired neuronal viability through its actions on TNFR1 (Barnum and Tansey, 2011). Consistent with these reports, astrocytic activation was delayed in mice lacking IL-1 receptor (Herr and Yong, 2001) addition, IL-1 upregulated nerve growth factor (NGF) and TGF-β in astrocytes at both gene level and protein level (Jauneau et al., 2006), which would be beneficial for recovery in the CNS. Besides, IL-18 plays an important role in activation of microglia and astrocytes. It has been reported that nerve injury induced a striking increase in IL-18 and IL-18 receptor (R) expressions in the dorsal horn and IL-18 and IL-18R were upregulated in hyperactive microglia and astrocytes respectively. The functional inhibition of IL-18 signaling pathways decreased the phosphorylation of nuclear factor kappa B (NFκB) in spinal astrocytes and the induction of astroglial markers (Miyoshi et al., 2008).

**Gliol cells, excitotoxicity and synapse function:** The astrocytic Ca\(^{2+}\) signaling and in particular the ability of astrocytes to propagate long distance Ca\(^{2+}\) waves probably contribute to the distant microglial activation (Nedergaard and Dirnagl, 2005). Ca\(^{2+}\) signaling in astrocytes is altered when astrocytes are challenged with inflammatory stimuli and they have become reactive. It is suspected that calcium waves propagated among activated astrocytes spread to distant areas and microglia far away from the injury affected site would be activated subsequently, producing proinflammatory cytokines (Hansson et al., 2010; Milligan et al., 2003; Watkins et al., 2003). The activation of glutamate receptors has also been found to induce the release of glutamate. Thus, a large build-up of glutamate can occur and induce a massive accumulation of Ca\(^{2+}\), leading to apoptosis and it was also noted that amyloid-beta (Aβ) plaques increase a neuronal vulnerability to excitotoxicity (Abeliovich et al., 1993). Aβ plaques, a pathological feature of AD, were found to induce depolarization of astrocytes, extracellular accumulation of glutamate and intracellular deposition of calcium ion Ca\(^{2+}\) (Otani and Ben-Ari, 1991). These changes usually include synaptic dysfunction and Ca\(^{2+}\) dysregulation (Foster, 2002) both of which can be precipitated in healthy young adult animals and/or in neuronal cultures in response to artificial elevations in TNF.

Astrocytes respond to ongoing synaptic activity by mobilizing intracellular Ca\(^{2+}\), leading to the release of pro-inflammatory cytokines such as IL-1β, TNF-α.
and IL-6. The inflammatory reactive glial cells can be neuroprotective by releasing anti-inflammatory cytokines, such as IL-10 and IL-4 (Milligan and Watkins, 2009). Achieving a balance between overproduction of pro-inflammatory cytokines and decreased production of anti-inflammatory cytokines may be one way to regulate an inflammatory response (Sloane et al., 2009). Activated astrocytes can also inhibit microglial activities and can exert inhibitory effect on microglia. Astrocytes also have been reported to decrease the production of NO, Reactive Oxygen Species (ROS) and TNF-α from microglia (Von Bernhardi and Eugenin, 2004; Smits et al., 2001; Tichauer et al., 2007). Thus the increased free radical generation, Nitric Oxide Synthase (NOS) gene expression may be activating microglia and astrocyte that may lead to the formation of proinflammatory cytokines ultimately leading to synaptic dysfunction which is an important pathophysiological component of AD (Bell and Claudio, 2006).

Glial activation, apoptosis and synapse function: Studies showing that glial activation, TNF-α and NF-κB Nuclear factor-kappa B activation modify long-term depression and potentiation of synaptic transmission in the hippocampus (Albensi and Mattson, 2000) provide further evidence that anti-apoptotic signaling can modulate synaptic plasticity. Finally, changes in mitochondrial membrane permeability in synaptic terminals have been associated with impaired synaptic plasticity in the hippocampus (Albensi et al., 2000), suggesting a role for apoptotic actions in synaptic function. Apoptosis plays a significant role in cell death during neurodegenerative disorders such as AD (Loh et al., 2006). A cascade of events like activation of caspases and aspartate-specific cysteine proteases has been proposed to play a key role in apoptosis (Nicholson and Thornberry, 1997; Kamat et al., 2011; Lee et al., 2005; Engidawork et al., 2001). Over activation of glutamate receptors can induce apoptosis by a mechanism involving calcium influx (Gluzner et al., 2000; Wong et al., 2002; Sastry and Rao, 2000; Gluzner et al., 2000). Biochemical mechanism involved in apoptosis can be activated in synaptic terminals, where it can alter synaptic function and promote localized degeneration of synapses (Mattson et al., 1999; Ivins et al., 1998). Apoptosis can be induced in synaptosome preparations and neuritis of cultured brain neurons by insults that induce apoptosis in intact neurons (Kamat et al., 2011).

NMDA receptor, neuroinflammation and synapse function: N-methyl-D-aspartate receptors (NMDARs) are located in neuronal cell membranes at synaptic and extra synaptic locations, where they are believed to mediate distinct physiological and pathological processes. Activation of NMDARs requires glutamate and a coagonist whose nature and impact on NMDAR physiology remain elusive. Glial cells are crucial regulators of synapse formation, elimination and plasticity. NMDA receptor activation also led to influx of calcium through a ligand- and voltage-sensitive calcium channel (Ascher, 1998), triggered significant advances in understanding the cellular cascades initiated as a result of tetanic stimulation. In addition, chronic NMDA administration to rat upregulate levels of proinflammatory IL-1β, TNFα, GFAP and iNOS (Inducible nitric oxide synthase) in rat brain (Chang et al., 2008; Kim et al., 2009). The glutamatergic hypothesis of AD states that glutamate related excitotoxic mechanisms involving the NMDA receptor lead to neurodegeneration and cell death (Bleich et al., 2008). The activation of glutamate receptors has also been found to induce the release of glutamate and induce a massive accumulation of Ca2+. This influx of Ca2+ contributes to an alteration of cell function, leading to cell death either through free radicals or through overload of the mitochondria, resulting in free radical formation, caspase activation and the release of apoptosis-inducing factors (Adams et al., 2000; Kamat et al., 2011). In vitro studies have begun to identify glial-derived synaptogenic factors, but neuron-glia signaling events during synapse formation in vivo remain poorly defined. Progressively accumulating evidence suggested that astrocytes play roles in synaptic transmission through the regulated release of synaptically active molecules including glutamate, purines (ATP and adenosine), GABA and D-serine (Perea et al., 2009; Shigetomi et al., 2008). Synaptic stimulation through NMDA receptors is important for learning and memory functions, but excess glutamate can over stimulate these receptors resulting into excitotoxicity and neurodegeneration (Michaels and Rothman, 1990). The release of such neurotransmitters occurs in response to changes in neuronal synaptic activity, involves astrocyte excitability as reflected by increases in astrocyte Ca2+ and can alter neuronal excitability (Halassa et al., 2007; Nedergaard et al., 2003). Such evidence has given rise to the ‘tripartite synapse’ hypothesis (Perea et al., 2009). Astrocytes play a role in the formation, maintenance and pruning of synapses during development (Christopherson et al., 2005). Astrocytes exerting a powerful influence on synaptic remodelling and pruning the healthy adult CNS or in response to CNS disorders (Barres, 2008). Cytokines such as tumor necrosis alpha (TNF-α) have been shown to influence homeostatic synaptic scaling by inducing the insertion of AMPA receptors at post-synaptic membranes (Stellwagen and Malenka, 2006). Although, it is not
certain whether astrocytes or microglia are primary sources of TNFα in the CNS in vivo, the effects on synaptic function of astrocytes derived growth factors and cytokines remain unclear. Activated astrocyte and microglia alters the NMDA receptor, free radicals, cytokine, apoptosis, neuroinflammation and their consequence on synaptic neurotoxicity which leads to AD like pathology (Fig 3).

Non steroid anti-inflammatory drug (NSAID) and AD: NSAIDs are inhibitor of cyclooxygenase (COX) isoenzymes that oxidize arachidonic acid to prostaglandin. The latter it activates G protein-coupled receptors, either directly or by acting as precursor for other eicosanoids which influence a variety of metabolic pathways (Choi et al., 2009). One such a classical pathway is COX-1 and COX-2- dependent activation of microglia resulting in release of pro-inflammatory and pro-oxidant factors that are injurious to nearby neurons or dendrites in experimental models (Sonnen et al., 2008). The relative contributions of COX-1 and COX-2 to such microglial-mediated paracrine damage are not entirely clear. However, COX-1 suppression (NSAIDs such as naproxen, ibuprofen) could protect neurons against such immune-mediated damage in the early stages of AD pathogenesis. By contrast, brain COX-2 is abundant in dendrites (Kaufmann et al., 1997), where it is essential for transduction of post-synaptic signals from NMDA-type glutamate receptors. Inhibition of COX-2 decreases the efficiency of such signaling (Manabe et al., 2004) and could therefore provoke increased presynaptic stimulation via autoregulatory mechanisms. The latter could conceivably stress neurons that are already dysfunctional in brains of patients with early AD, or late-stage pre-symptomatic AD. Recent findings demonstrate that selective COX-1 inhibition reduces neuroinflammation, neuropathology and improves cognitive function in 3×Tg-AD mice. COX-1, classically viewed as the homeostatic isoform, is localized in microglia and is actively involved in brain injury induced by pro-inflammatory stimuli including Aβ, lipopolysaccharide and interleukins (Choi et al., 2013). Clinical studies involving anti-inflammatory drugs in AD highlight the need to better understand and describe the mechanisms leading to inflammation in the diseased brain, as well as the pathways affected following its activation.

CONCLUSION

It seems that glial activation plays an important role in AD neurotoxicity as evidence by progressively accumulating data. But still so many questions are to be answered to understand its role in AD. Is glial activation secondary to the AD process or does glial activation directly contributes to it. Other issues to consider are that the microglia and astrocytes can have both neuroprotective and neurodestructive functions making it difficult to firmly place their role in the AD disease
process. It is evident from broad studies that glial activation caused NMDA receptor activation, free radical generation, excitotoxicity and synaptic dysfunction which are contributory factors in AD pathology.

**Therapeutic targets and future directions:** It is becoming more generally appreciated that a drug targeting peripheral inflammation may not be the most appropriate therapeutic for neuroinflammation and that a new paradigm starting with a focus on selective modulation of activated glia mechanisms relevant to disease is needed. The evidence provide a novel integrative proof in support of the neuroinflammation hypothesis of disease progression, demonstrate that neurodegeneration can be attenuated by targeting innate brain proinflammatory cytokine responses and indicate the feasibility of developing efficacious, safe and selective therapies for neurodegenerative disorders by targeting key glial activation pathways. As evidence from several studies that glial activation leads to synaptic neurotoxicity and neurodegeneration in AD. So, in our opinion targeting the glial activation pathways linked synaptic neurotoxicity will be the better therapeutic approaches in AD like neurodegenerative disorders.

**ACKNOWLEDGMENT**

Financial support to Shivika Rai from council for scientific and industrial research (CSIR) is gratefully acknowledged.

**REFERENCES**


Jameau, A.C., A. Ischenko, A. Chatagner, M. Benard and P. Chan et al., 2006. Interleukin-1β and anaphylatoxins exert a synergistic effect on NGF expression by astrocytes. J. Neuroinflammation., 10.1186/1742-2094-3-8


