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

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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

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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-/-astrocytes (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

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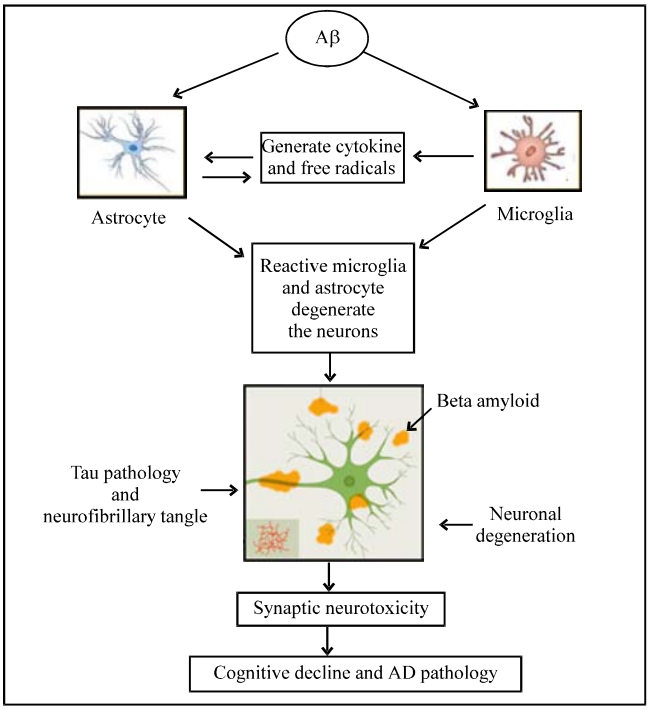

Fig. 1: Flow diagram of graphical abstract depicts the mechanism of glial activation and further effects on synapse dysfunction mediated AD pathology

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 (Verkhratsky and Steinhauser, 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 (Shaftel *et al*., 2007). Astrocytic activation which leads to astrogliosis 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 (Albrecht *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; Crehan *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, proinflamatory cytokines and other foreign particles presents 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) (Chavarria and Alcocer-Varela, 2004). Microglia migrates 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 (Minghetti *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-êB) 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 (Kam and See, 2000).

Glial 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 astrocytes 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 astrocytes 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 leads to formation of proinflammatory cytokine 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) which triggers the neuronal damage (Liu *et al*., 2003). The activation of microglia releases proinflamatory 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. Proinflamatory 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-ã, 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) B_1R activation also plays an important role in limiting the accumulation of Aβ in AD-like brain, likely through 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-Gfa2 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 astrocytes 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 astrocytes 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 3xTg-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

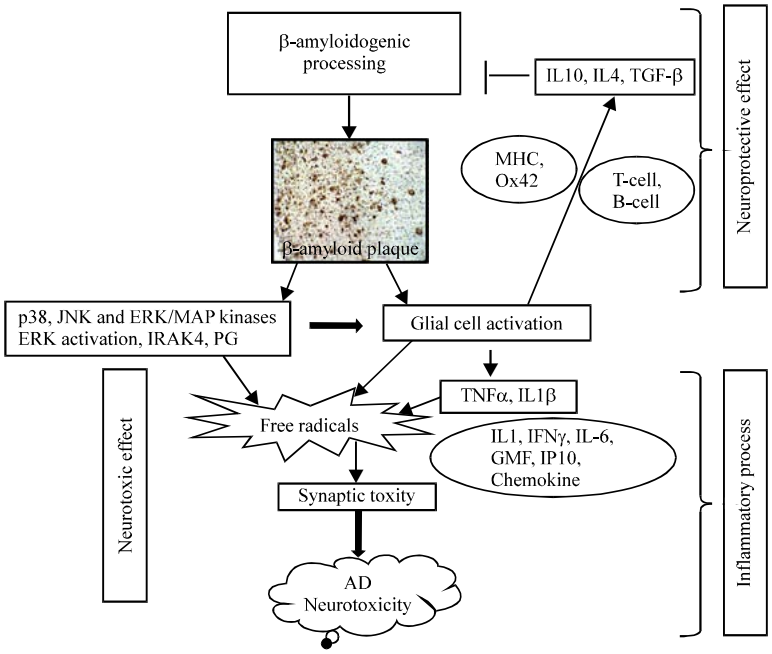

Fig. 2: Schematic diagram depicting the involvement of kinases and proinflammatory mediator's protein in Aβ induced glial activation and kinases which are associated with AD pathology

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 (Herx 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 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).

Glial 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 neurons 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-a 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 (Glazner *et al*., 2000; Wong *et al*., 2002; Sastry and Rao, 2000; Glazner *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-1b, TNFa, 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*., 2003). 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 gliotransmitters 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-a) 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

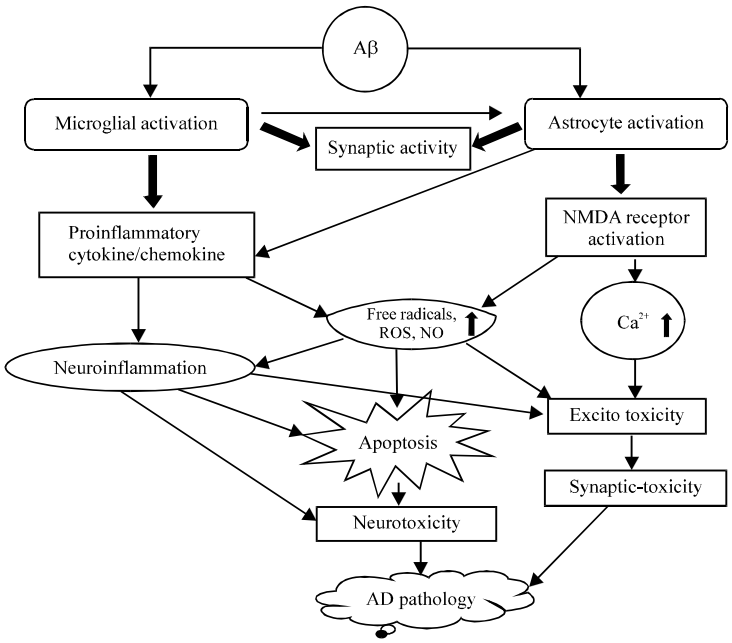

Fig. 3: Representative pictorial diagram shows the effect beta amyloid on glial activation and their association with synaptic neurotoxicity which ultimately causes the AD pathology

certain whether astrocytes or microglia are primary sources of TNFa 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 Aß, lipopolysaccharide and interleukins (Choi *et al*., 2013). Clinical studies involving antiin?ammatory drugs in AD highlight the need to better understand and describe the mechanisms leading to in?ammation 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.

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