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Tumor Necrosis Factor and Alzheimer's Disease: A Cause and Consequence Relationship

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ABSTRACT:
Tumor necrosis factor and alzheimer's disease: a cause and consequence relationship

Tumor necrosis factor alpha (TNF) was discovered more than a century ago as endotoxin-induced glycoprotein, which causes haemorrhagic necrosis of sarcomas. Originally described as a circulating factor that causes necrosis of tumours,it now appears that TNF has diverse and critical roles to play in the pathogenic progression of a number of chronic inflammatory disorders, including rheumatoid arthritis, Crohn's disease, psoriasis, Alzheimer's disease, ischemic stroke, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. A pivotal role has emerged for TNF as an important contributor to Alzheimer's disease pathology, as TNF appears to modulate several neuropathological mechanisms in Alzheimer's disease. Evidence for the involvement of TNF in Alzheimer's disease pathology and neuronal loss comes from studies of TNF over-expression, TNF localization studies, multiple relationships between TNF and amyloid β-peptide (Aβ), interactions between TNF and the microtubule-associated tau protein, TNF-mediated apoptotic cell death, and association of TNF with several neurotransmitters linked to Alzheimer's pathology. This review presents TNF as a neuromodulator in pathological progression of Alzheimer's disease by linking it with several endogenous mediators and advocates its status as a current therapeutic target in the quest to find a cure for Alzheimer's disease.

Key words: Alzheimer's disease, Amyloidβ, TNF, apoptosis, iNOS, MAPK, NGF

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ALZHEIMER'S DISEASE-- AN INFLAMMATORY DISORDER

Diseases are characterized by dysregulation of biological pathways (1) that can result from infections, environmental factors, genetic mutations, or lifestyle. Such dysregulation alters the expression of proteins in multiple cellular pathways, leading to changes in growth, differentiation, or apoptosis (2).

Alzheimer's disease (AD) is an untreatable (3), multifactorial, chronic, progressive, neurodegenerative disorder which is the principal cause of dementia throughout the world and the fourth cause of death in developed economies after cancer, cardiovascular diseases, and vascular stroke (4). AD is characterised by three primary groups of symptoms. The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (i.e. loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric and behavioural disturbances such as depression, hallucinations, delusions, and agitation, collectively termed as non-cognitive symptoms (5).The third group comprises difficulties with performing activities of daily living (deemed "instrumental" for more complex activities such as driving and shopping and "basic" for dressing and eating unaided).

The two major hallmarks of AD are neurofibrillary tangles (NFT) and senile plaques (SP). The former are composed of paired helical filaments (PHFs) made of hyperphosphorylated tau proteins and the latter are made up of a core of aggregated amyloid-ß (Aß) peptides surrounded by reactive glia.The deposition of amyloidß protein in brain areas involved in cognitive functions is assumed to initiate a pathological cascade that results in synaptic dysfunction, synaptic loss, and neuronal death (6). Recent evidence suggests an inflammatory component in AD which is characterized by astrogliosis, microgliosis, cytokine elevation, and changes in acute phase proteins (6,7). Inflammation has been found to play a critical role in a variety of chronic diseases, including type 2 diabetes

(8), metabolic syndrome (9),obesity (10), depression (11), and neurodegeneration (12).

AD, a multifarious, complex syndrome has also shown immunological disturbances and this underlines the importance of immunological imbalance in the explanation of the etiopathogenesis and progress of AD. In AD, changes in the central nervous system (CNS) respond well to immunomodulatory treatment and the results so far point to an important role of the immune system in the development of disease symptoms and in the progression of the clinical state of AD patients (13,14).

The cytostructural changes in AD are caused by three mechanisms which explain the part played by immune processes in the development of disease symptoms. These are: (i) abnormal immune reactions in the form of autoimmunity directed against the components of the brain tissue (13,15); (ii) local immune reactions caused by brain tissue damage; these normal immune reactions are intensified locally in brain tissue leading to further structural and functional damage to the CNS (16,17); and (iii) disturbances of immunocytokine secretion (excessive secretion and deposition of INF-gamma, TNF, IL-1, IL-2, IL-6 around Aß are found) (18).

INFLAMMATION AND THE IMMUNE SYSTEM - CROSS TALK IN AD

For many decades the general consensus was that the immune system and the CNS were relatively independent due to the inaccessibility of the brain to the immune cells because of the blood-brain barrier. This opinion has changed and it has become apparent that many immune molecules are used by the nervous system in intercellular communication (19). In the brain, inflammation is mediated largely by glial cells, the support cells of the nervous system. Glial cells include astrocytes, which support neuronal metabolism, oligodendrocytes which produce myelin insulation for nerve cells (allowing more efficient conduction of nerve impulses), and microglia, which serve as a kind of immune system. Glial cell activation is a key feature of brain inflammation. When activated, microglia produce inflammatory mediators that activate more cells to produce additional inflam matory mediators. These mediators can thus create positive feedback loops, thereby amplifying inflammation. Brain inflammation, including increased microglia and astrocyte activation, generally increases as part of the aging process and brain inflammation is a key feature of neurodegenerative diseases, including AD (20).

The immune system comprises a complex interrelated network of cellular, molecular, and chemical mediators that function to protect the body against environmental stress factors. These stressors can be as diverse as microorganisms (viral, bacterial, fungal agents), physical damage (burns, lacerations), or environmental toxins (snake venoms, nonessential metals, chemicals). To combat all these stressors, the first line of defense is innate or natural immunity. The inflammatory component of this response is important in recruiting cells of the immune system to the compromised area, and cytokines and chemokines mediate this function. Cytokines orchestrate a specific response that is appropriate based on the type of foreign antigen that has penetrated the tissue, and chemokines are important in allowing cells of the immune system to reach the area under attack (3).

The innate immune response in the CNS is necessary to resolve potential pathogenic conditions. It is usually short-lived and ensures that the stress factor is removed. Transient upregulation of inflammatory events in the brain is natural and does not lead to neuronal cell death (23).

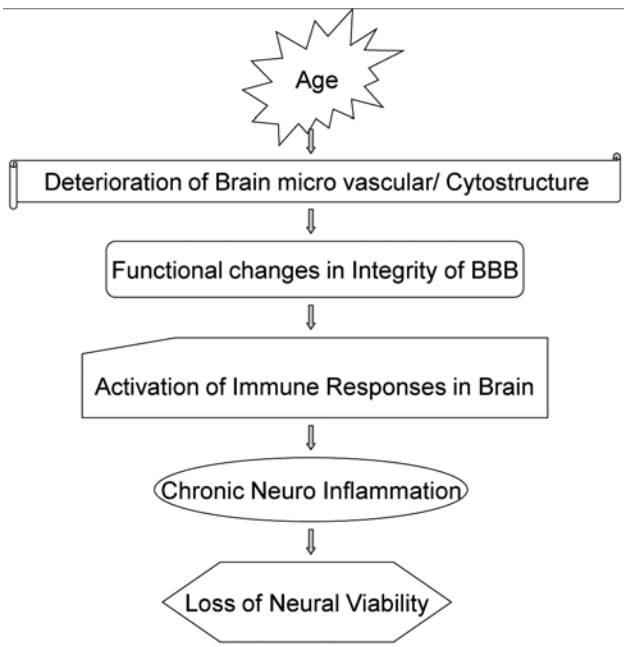

Figure 1: Age associated neuronal viability
As the brain ages, inflammatory events are upregulated (21,22) due to compromise of the blood-brain barrier (BBB) which may occur as a result of senescence, leading to activation and proliferation of both microglial and astrocytic cells.

This is because endogenous factors such as glucocorticoids moderate this response by inhibiting proinflammatory gene expression via negative feedback (24). However, over activation of innate immunity can lead to neurodegeneration (3). Proinflammatory cytokines and chemokines (e.g.,TNF, IL-1, and MCP-1) have been implicated as etiological factors in a variety of neurological disease states including AD (25,26). TNF is prominent among proinflammatory cytokines known to be associated with neuropathological effects underlying several neurodegenerative disorders (27,28).

CYTOKINES IN THE BRAIN

The first cytokine was discovered by Beeson in 1948 (29) as a pyrogenic compound extracted from polymorphonuclear leucocytes and was later known as IL-1β. Since then, many other cytokines have been discovered, and these fall into five main categories: interleukins, interferons, tumor necrosis factors, growth factors, and chemokines (30).

Cytokines are low molecular weight soluble glycoproteins that are secreted mainly, but not exclusively, by immunological cells such as T-cells, macrophages, and neutrophils. Other cells that secrete cytokines include keratinocytes and dendritic cells of the skin (31) and Schwann cells and glial cells of the CNS (32,33).

Cytokines are nonimmunoglobulin in nature, released by living cells of the host, and act non-enzymatically in picomolar to nanomolar concentrations through specific receptors to regulate host cell function. Cytokines are pleiotropic in their biological activities and play pivotal roles in a variety of responses, including the immune response, hematopoiesis, neurogenesis, embryogenesis, and oncogenesis. The main types of cytokines are lymphokines, interleukins, monokines, TNFs, interferons, colony-stimulating factors, transforming growth factors, peptide growth factors, heat shock and other stress proteins. Cytokines have been classified on the basis of their biological responses into pro- or anti-inflammatory cytokines, depending on their effects on immunocytes. TNF, interleukin (IL)-1, IL-6, IL-7, IL-8, IL-12, IL-15, IL-17, IL-18, IL-23, lymphotoxin, macrophage migration inhibitory factor, resistin, interferon-γ, granulocyte-macrophage colony stimulating factor, macrophage colony-stimulating factor, fibroblast growth factor and vascular endothelial growth factor are proinflammatory cytokines,whereas IL-1Ra, IL-18 binding protein, IL-10, transforming growth factors, IL-11, IL-13, osteoprotegerin and adiponectin are anti-inflammatory cytokines. IL-22 and oncostatin M are equivocal (34).

Cytokine synthesis is prompt and their actions are often localized with a relatively short half-life. This distinguishes them from hormones which are constantly produced with longer-lasting and more distant effects.

TNF --AN INTRODUCTION

In 1891, the success story of William Coley in using supernatant extract of heat-killed mixtures of Streptococcus pyogenes and Serratia marcescens bacteria to treat tumors may in fact be the first discovery of TNF(35), although it was identified in 1975 as an endotoxin-induced glycoprotein which caused haemorrhagic necrosis of sarcomas that had been transplanted into mice (36). Human TNF was cloned in 1985 (37) and recombinant TNF was shown to induce haemorrhagic necrosis of transplanted methylcholanthrene-induced sarcomas in syngeneic mice.

TNF is a non-glycosylated protein of 17 kDa with 157 amino acids and belongs to a family of peptide ligands that activate a corresponding set of structurally related receptors (38, 39). It belongs to a super family of ligand/receptor proteins called the TNF/TNF receptor (TNF/TNFR)superfamily proteins. TNFRs are either constitutively expressed (TNFR1, p55-R) or inducible (TNFR2, p75-R) (40). TNF possesses a trimeric symmetry with a structural motif called the TNF homology domain (THD), which is shared with all other members of the TNF proteins. This THD binds to the cysteine-rich domains (CRDs) of the TNFRs, and variations of these CRDs lead to heterogeneity of the TNFRs (41).

There are roughly 20 ligand receptor pairings now recognized for the TNF superfamily, with a modest degree of crosstalk (i.e. multiple ligands signaling through one receptor, or a single ligand signaling through multiple receptors) (42).

TNF is a key signalling protein in the immune system. As a regulatory cytokine, TNF orchestrates communication between immune cells and controls many of their functions (43). TNF is best known for its role in leading immune defenses to protect a localized area from invasion or injury, but it is also involved in controlling whether target cells live or die (44).

TNF is produced predominantly by activated macrophages and T lymphocytes as a 26 kDa protein, pro-TNF, which is expressed on the plasma membrane, where it can be cleaved in the extracellular domain by the matrix metalloproteinases, resulting in the release of a 17 kDA soluble form. Both membrane-associated and soluble TNFs are active in their trimeric forms, and the two forms of TNF may have distinct biological activities. TNF converting enzyme (TACE, also known as ADAM-17) mediates release of TNF from the cell surface (45), but is involved in processing several cellmembrane-associated proteins, including TNF receptors, which are released by its action to produce soluble forms that can neutralize the actions of TNF (46). TACE may therefore be either pro-or anti-inflammatory, depending on whether it acts on an effector (e.g. macrophage) or target (e.g. endothelial) cell, releasing ligand or receptors, respectively (47).

TNF largely relies on TNFR1 for apoptosis and on TNFR2 for any function related to T-cell survival. However, there is some degree of receptor crosstalk and overlapping function, depending on the activation state of the cell, among a host of other factors (48).

BIOLOGICAL ROLE OF TNF

TNF is thought to play a central role in the self-propagation of neuroinflammation (49). TNF plays a critical role in brain development, brain physiology, synaptic plasticity, sleep, circadian rhythm and normal behaviour (50). In the CNS, TNF is produced primarily by microglia and astrocytes in response to a wide range of pathological processes, including infection, inflammatory disease, ischaemia, and traumatic injury (51). However, TNF has been shown to have both harmful and beneficial effects in the injured brain (52). Inhibition of TNF ameliorates ischaemic brain injury in mice (53), whereas mice lacking TNF are highly susceptible to experimental autoimmune encephalomyelitis (54). TNFR2 has been shown to promote proliferation of oligodendrocyte progenitors and remyelination in a murine neurotoxin-induced model of demyelination (55).

The biological function of TNF-α includes the modulation of growth differentiation and proliferation of a variety of cell types, but it is also important in the causation of apoptosis. TNF binding to TNFR1 activates apoptosis through two pathways, involving the adaptor proteins TNFR1-associated death domain (TRADD) and associated death domain (FADD). By contrast, TNFR2 signalling involves the mobilization and nuclear entry of the transcription factor, nuclear factor-κB (NF-κB), to promote transcription of pro-survival genes (44).

Further, TNF has several pre-eminent roles during normal development: it shapes the efficacy of the immune system and guards against infectious diseases, cancer and autoimmune diseases (56). TNF facilitates the proliferation of immune cell clones, especially of T cells, to counter a pathological infection or invasion. They also allow the differentiation and recruitment of naive immune cells to continue waging the battle, as well as the destruction of superfluous immune cell clones to limit internal inflammation and tissue damage once the infection or invasion has resolved. To carry out this complex array of functions, TNF acts on the two receptors, TNFR1 and TNFR2, generally relying on TNFR2 for any function related to T-cell survival and on TNFR1 for apoptosis (44).

THE ROLE OF TNF IN AD

The first indication of a contribution of TNF signalling to AD came from the identification of the presence of TNF at amyloidogenic plaques in post-mortem analysis of AD brains (57) and this prompted investigations into the association between AD and TNF and its receptors (58). The genetic association between the TNF receptors (TNFR1 and TNFR2) and AD revealed that genes for TNFR1 and TNFR2 reside on chromosome 1p and chromosome 12p, respectively, and these regions show a genetic linkage to late-onset AD (49). The discovery of up-regulation of TNF-α in the brain and plasma of AD patients and up-regulation of TNFR1 in the AD brain further consolidated the relationship among them (26, 59).

Brain oxidative stress seems to exert an important role in the cognitive impairment observed in AD. The expression of inducible nitric oxide synthase (iNOS) and NO synthesis has been deeply associated with AD pathology. In this context, it has been demonstrated that both iNOS expression and peroxynitrite damage take place in the AD brain (60,61). Aß induces cognitive deficits through several mechanisms and one of them is through iNOS. Nitric oxide (NO) is synthesized from L-arginine by the enzymes NO synthases [endothelial, neuronal and an isoform expressed during inflammatory reactions

(iNOS)]. iNOS is an enzyme expressed after exposure of cells to several noxious agents such as cytokines or LPS (62). Medeiros et al. suggest that TNF and iNOS signalling pathways are linked and have an important role in the cognitive deficits observed in the earlier stages of AD (63). In the CNS, iNOS is not commonly found in healthy tissues, but it can be expressed after brain insult in astrocytes, neurons, and endothelial cells, where it triggers the production of high amounts of NO (64).

iNOS generates NO and NO-derived reactive nitrogen species such as peroxynitrite. Accumulation of highly reactive molecules induces lipid peroxidation, tyrosine nitrosylation, DNA oxidative damage, and neuronal disruption, which are common characteristics of the AD brain (65). Interestingly, these events seem to be modulated by TNF. Also, Aß has been shown to interact in a synergistic manner with cytokines to induce neuronal damage via reactive oxygen species (ROS)- and NO-dependent pathways (66,67).

Production of iNOS protein is tightly regulated at the transcriptional level, but the upstream signaling events mediating Aß-induced iNOS expression remain poorly understood. Molecular cloning and analysis of the promoter region of the iNOS gene revealed the presence of binding sites to several transcriptional factors, such as AP-1, NFKB, and TNF response element (68). Furthermore, iNOS induction by Aß1–40 depends on TNFα signaling, with involvement of JNK/c-Jun and NFKB. These results also extend the notion that iNOS protein represents an unusual enzyme that can be modulated by highly specialized mechanisms.

Overproduction of NO may lead to neuronal damage and death. The predominant mechanism by which NO promotes neuronal toxicity implicates the reaction of NO with superoxide anion to generate the cytotoxic substance peroxynitrite (64,69). Under physiological conditions, highly reactive molecules are rapidly eliminated by antioxidant enzymes, including GPxs (70). However, in pathological conditions, excessively accumulated reactive species induce several cellular dysfunctions.

STRESS, TNFα AND ALZHEIMER'S DISEASE

Besides NO, stress also plays a critical role in progression of neurodegenerative conditions like AD. In fact, stress causes deficits especially in spatial memory performance and this effect may be important for pathophysiological processes connected with aging, as well as degenerative diseases such as AD (71). Moreover, the aging hippocampus apparently is more susceptible to stress, and this vulnerability may be increased in AD (72). Long-lasting stress affects synaptic plasticity, dendritic morphology and neurogenesis in animals, and induces both clinical and anatomical features of neurotoxic damage in humans (73).

The COX pathway has also been implicated in stress-induced brain damage. COX-2 is induced in stress and has been involved in the damage associated with this condition. Similar to iNOS, the promoter of the immediate-early gene COX-2 depends on the activation of NFκB in stress. Both enzymatic sources of oxidative mediators in the brain depend on the activation of the NMDA glutamate receptor, and in the case of iNOS, its activation also depends on the release of TNF (73).

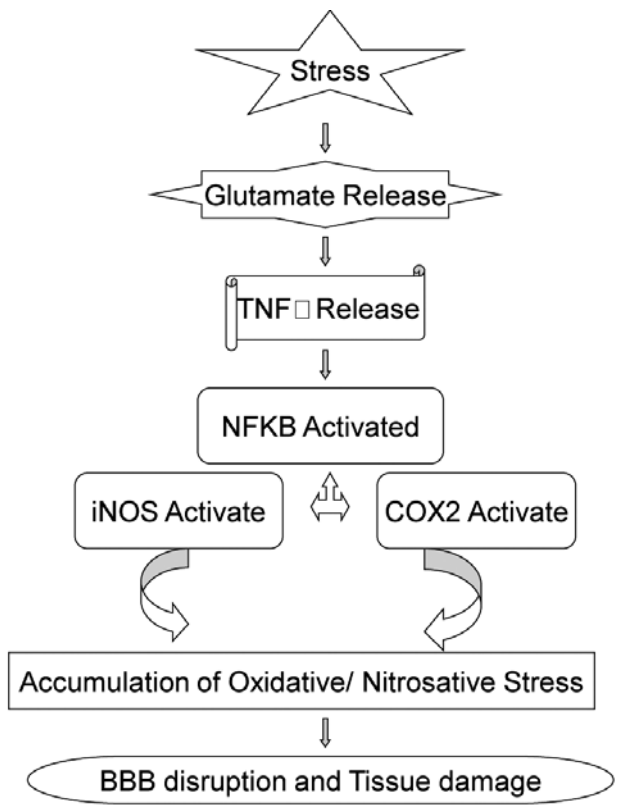

Figure 2: Stress-induced oxidative/nitrosative mediators in thebrain
TNF = tumor necrosis factor alpha; iNOS = inducible nitricoxide synthase; COX-2 = cyclooxygenase-2; BBB = blood-brain barrier.

TACE expression and activity have been found to change in some neuroinflammatory conditions in which an increase in TNF levels has been described. The predictable consequence of TACE activation is a larger release of TNF. In fact, this has been found in brain cortex samples obtained from stressed rats. TNF has been identified also as a main regulator of persistence of oxidative changes after sustained, inescapable and predictable stress (73). It is well known that one of the main effects of the stress response is the release of large quantities of excitatory amino acids, such as aspartate and glutamate (74). Released glutamate can bind to different receptors, the main one being the NMDA subtype, whose activation causes the mobilization of free cytosolic calcium. Excess intracellular calcium concentration over-activates certain calcium-dependent enzymes, resulting in the generation of oxygen radicals, protein misfolding and cytoskeletal damage (75), constituting the process known as excitotoxicity.

Both neurons and astroglia are capable of transporting glutamate by a high-affinity, sodium-dependent transport. To date, high-affinity, sodium-dependent glutamate transporters known as excitatory amino acid transporters (EAATs) 1 to 5 have been cloned from rodent and human tissue (76). Immunohistochemical studies have revealed that EAAT1 and EAAT2 are present primarily in astrocytes, while EAAT3 and EAAT4 are distributed in neuronal membranes, and EAAT5 is retinal. Indeed, stress causes a decrease in synaptosomal glutamate uptake, indicating a dysfunction of glutamate transporters at this level (77). Furthermore, glutamate transporter (EAAT2 and EAAT3) expression in brain cortical membranes is decreased after stress, possibly explaining the increase in basal serum glutamate release detected in stressed animals (78).

TNF, APOPTOSIS AND AD

Apoptosis is regarded as an important component in cell death.This mechanism of programmed cell death is upregulated in AD, and activation of programmed cell death seems to rely on the TNF signalling pathway. TNFR1 contains a cytoplasmic death domain (DD) that binds to adaptor TRADD (TNFR-associated DD), which indirectly activates caspase cascades, causing apoptosis (79). In this context, it has been suggested that Aß1–40 binds directly to TNFR1, resulting in neuronal apoptosis (59).

Among the many regulatory steps in brain development is the process of elimination of differentiating neu¬rons at certain stages of maturation known to occur through an intrinsic suicide program known as apoptosis. In addition to this, apoptosis is an additional death process induced by pathophysiological stimuli during development as well as in adulthood. Apoptosis describes a cell death pathway utilized by many, if not all, developing cells in the nervous system, but it may also be activated at the same time as a consequence of acute or chronic pathological impulse (80,81). Extensive neuronal loss occurs in AD brains, and it has been speculated that deregulation of apoptotic death pathways is etiologically responsible for the disease development (82).

During apoptosis the neuronal cell body shrinks, plasma membrane blebbing occurs, and the nuclear DNA becomes condensed and fragmented; the integrity of organelles (mitochondria and endoplasmic reticulum) is maintained until very late stages of the cell death process. In contrast, neurons undergoing necrosis swell and lyse. Biochemical features of apoptosis include loss of plasma membrane phospholipid asymmetry, maintenance of ATP levels, activation of one or more cysteine proteases of the caspase family, mitochondrial membrane depolarization, mitochondrial oxyradical production and calcium overload, and release of factors from mitochondria that can induce nuclear chromatin condensation and DNA fragmentation (83,84). Neuronal apoptosis occurs during development of the nervous system (85) and in many different neurodegenerative disorders including AD (86,87).Triggers of neuronal apoptosis include trophic factor withdrawal (88), oxidative insults (89), metabolic compromise (90) and over-activation of glutamate receptors (91).

In addition, caspases are closely associated with induction of the apoptotic cascade, and activation of caspase-3 is both necessary and sufficient to trigger apoptotic cell death in response to elevated Aß in AD (92). Unlike calpain, which is associated with both necrotic and apoptotic cell death, caspase-3 is exclusively characteristic of apoptosis-like cell death (93). In addition, Aß-induced caspase-3 activation causes abnormal processing of the microtubule-associated protein tau in models of AD (94,95). Aß-induced neurotoxicity is associated with increased activity of caspase-3, and this is exacerbated in the presence of astrocytes. Activated forms of caspase-3 are found in AD brain (96). Activation of caspase-3 precedes Aß-induced neuronal death in primary cortical

cultures. The mechanism underlying astrocyte-mediated increased caspase-3 activation in response to Aß can be attributed to factors that are secreted from astrocytes or direct neuron–astrocyte interactions. Soluble factors released by astrocytes bind to neuronal plasma membrane receptors, inducing various cell signalling pathways. For example, when secreted from astrocytes, TNF binds to neuronal Cd120a/b receptors triggering caspase activation through death effect or domains (97).

Most neurons in the mammalian CNS possess receptors for another trigger of apoptosis, the excitatory neurotransmitter glutamate. Over-activation of glutamate receptors can induce apoptosis by a mechanism involving calcium influx (98) and such 'excitotoxicity' may occur in neurodegenerative conditions such as AD (99). One mechanism through which TNF-α is neurotoxic is by over-stimulation of the glutamate receptors such as the NMDA receptor (100). Excitotoxicity in general is linked to excessive glutamate activation of receptors, particularly the NMDA receptor. Cell death resulting from excessive levels of glutamate and over-stimulation of glutamate receptors is known to be caused by impaired uptake of glutamate by glial cells (101). Stimulating rat primary cultured microglial metabotropic glutamate receptors (mGluRs) for 24 h induces microglial activation which in turn induces caspase-3 activation in cerebellar granule neurones in culture. This neurotoxicity is mediated by TNF released by the microglia via neuronal TNF-R1 and caspase-3 activation (102).

TNF AND ROLE IN SYNAPTIC PLASTICITY

TNF is known to act as a regulator of synaptic plasticity. TNF levels are elevated in several neuropathological states that are associated with learning and memory deficits (102), including AD. TNF has been shown to regulate the development of the hippocampus, as TNF-R1 and TNF-R2 knockout mice demonstrate decreased arborization of the apical dendrites of the CA1 and CA3 regions and accelerated dentate gyrus development (103), probably via activation of TNF-R2, which does not lead to caspase-3 activation but is known to transduce the trophic effect of TNF (104).

Long-term potentiation (LTP) is widely considered one of the major cellular mechanisms that underlie learning and memory (105,106). In neuroscience,LTP is a long-lasting enhancement in signal transmission between two neurons that results from stimulating them synchronously. It is one of several phenomena underlying synaptic plasticity, the ability of chemical synapses to change their strength. Memories are thought to be encoded by modification of synaptic strengths (106).

Two forms of synaptic plasticity seen in the hippocampus, LTP and long-term depression (LTD), involve glutamate receptor activation and increased intracellular calcium levels, with induction of LTP dependent on the activation of calcium–calmodulin kinase II, protein kinase C (PKC) and PKA, and with induction of LTD dependent on activation of serine/threonine phosphatases 1,2A and 2B (107,108). LTP is a long-lasting increase in synaptic efficacy, which is thought to be an important underlying mechanism of learning and memory formation (106).

The stability and cycling of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) glutamate receptors at synapses has been shown to be an essential process in both LTP and LTD (109,110). Since TNF has been shown to up-regulate AMPA receptors (111) it has been postulated that TNF might serve an essential function in Hebbian synaptic plasticity and possibly learning and memory. Research by Tancredi et al. (112) and Cunningham et al. (113) has demonstrated that pathophysiological levels of TNF inhibit LTP in the dentate gyrus of rat hippocampal slices. TNF markedly influenced synaptic efficacy by upregulating surface expression of AMPA receptors which is mediated through TNFR1 and phosphatidylinositol 3 (PI3) kinase-dependent processes. Inhibition of early phase LTP by TNF is dependent on a p38 mitogen-activated protein kinase process, whereas late phase LTPinhibition is p38 MAPK-independent (114).

It has also been shown that application of TNF causes an increase in RGS7 (a regulator of G-protein signaling) and that this increase is dependent on activation of p38 MAP kinase (115). The RGS7 protein modulates G-protein signaling by accelerating the intrinsic GTPase activity of Gαi and Gαq subunits. Increased RGS7 levels therefore lead to increased Gαq levels, giving rise to increased calcium levels. Combined with the aforementioned, evidence from Stellwagenet al. (116) that TNF causes increased expression of AMPA receptors which may be more calcium permeable, the intracellular calcium

concentrations may become sufficiently elevated in the presence of TNF to contribute to the impairment of LTP. mGluRs may also play a role in the inhibitory effects of TNF on early LTP. We have recently shown that inhibition of mGluR1 and mGluR5 can block the TNF-dependent inhibition of early and late LTP (114). Activation of these subtypes of mGluRs would also lead to an increase in intracellular calcium concentration. Thus a complex and as yet undiscovered interaction between TNF and mGlu receptors and the p38 MAP kinase would be required for inhibition of LTP to occur (102).

TNF, NERVE GROWTH FACTOR AND A CHOLINERGIC CONNECTION

The cholinergic system plays an important role in memory formation and retrieval. The hippocampus, amygdala and cortical regions of the brain are mainly involved in cholinergic transmission to monitor learning and memory processing and seem to be more prone to oxidative damage and involved in the pathogenesis of AD (117). One of the most fundamental and consistent features of AD is the severe degeneration of cholinergic neurons projecting from the basal forebrain to cortical and hippocampal areas (118,119). A 90% loss of basal forebrain cholinergic neurons has been found in AD patients (120).

Nerve growth factor (NGF) is the first discovered and best characterized member of a family of neurotrophins which includes brain derived neurotrophic factor, neurotrophin 2 and neurotrophin 3/4 (121,122).The biological activity of NGF is mediated by two receptors, namely p75, a low affinity receptor which binds to all neurotrophins and TrkA a high affinity tyrosine kinase receptor which is thought to mediate the biological actions of NGF (123). Within the CNS, NGF stimulates growth and differentiation of forebrain cholinergic neurons located in the septum and in the nucleus basalis of Maynert which receive trophic support from the hippocampus and cortex respectively (124).

Impairments in NGF transport from the cortex to the basal nucleus and from the hippocampus to the septum decrease the synthesis of choline acetyltransferase (ChAT), the number of forebrain cholinergic neurons and alter behavioral performances associated with learning and memory processes (125,126).

TNF in brain promotes NGF synthesis through a dose-dependent mechanism. Under basal conditions, TNF maintains the concentration of brain NGF (cortex), and high concentrations may cause cell damage and down-regulation of NGF (hippocampus), whereas optimal pharmacological doses of TNF promote NGF synthesis (hypothalamus). One implication of this hypothesis is that supra-normal levels of TNF may be associated with neuronal damage, while optimal endogenous availability is associated with a stimulatory effect on NGF synthesis and release (127).

CONCLUSIONS

Immunization as one of the approaches in treatment of AD has led to an increased interest in the immune processes associated with this disease and highlighted their role in AD pathogenesis. Receptor binding of TNF stimulates a variety of intracellular signaling pathways that have been implicated in AD, including the activation of protein kinase C, c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (p38/MAPK), PI3 kinase, extracellular signaling-related kinase (ERK), as well as activation of caspase-1 and -3; these effects make it a versatile molecule involved in the cross talk of pathological signaling in AD.

This review provides evidence that TNF mediates essential nervous system functions like synaptic plasticity, apoptosis, neurogenesis, and other biological functions at the molecular level and influences cellular mechanisms serving learning, memory, and cognition under physiological conditions. However under pathological conditions the same TNF may become a scavenger for neuronal cells and lead to cholinergic dysfunction, oxidative and nitrosative stress, activation of caspase, and effects on hyperphosphorylation of tau and amyloid ß-induced cell death. This review advocates significant involvement of TNF in healthy states as well as in chronic neuropsychiatric states like AD. From scientific, clinical, and commercial perspectives, TNF is undoubtedly one of the major successes of rational drug design targeting, and TNF blockers are now the best-selling class of biologics. The three established anti-TNF biologics (Enbrel, Remicade, and Humira) combined for over US$ 16 billion in sales in 2008 and in contrast to other biologic blockbusters such as erythropoietin, the TNF market is among the fastest growing.

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