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INVITED REVIEW

Divergent Roles for Tumor Necrosis Factor-α in the Brain

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Abstract Proinflammatory cytokines and chemokines have been implicated in the pathogenesis of several neurological and neurodegenerative disorders. Prominent among such factors is the pleiotropic cytokine, tumor necrosis factor (TNF)-α. Under normal physiological conditions, TNF-α orchestrates a diverse array of functions involved in immune surveillance and defense, cellular homeostasis, and protection against certain neurological insults. However, paradoxical effects of this cytokine have been observed. TNF-α is elicited in the brain following injury (ischemia, trauma), infection (HIV, meningitis), neurodegeneration (Alzheimer's, Parkinson's), and chemically induced neurotoxicity. The multifarious identity for this cytokine appears to be influenced by several mechanisms. Among the most prominent are the regulation of TNFα-induced NF-κB activation by adapter proteins such as TRADD and TRAF, and second, the heterogeneity of microglia and their distribution pattern across brain regions. Here, we review the differential role of TNF-α in response to brain injury, with emphasis on neurodegeneration, and discuss the possible mechanisms for such diverse and region-specific effects.

Keywords brain · brain injury · cytokines · microglia · neurodegeneration · neurotoxicity · region specificity · TNF-α · tumor necrosis factor

Abbreviations

3-NP	3-nitropropionic acid
6-OHDA	6-hydroxydopamine
Aβ	amyloid beta peptide
AD	Alzheimer's disease
BBB	blood–brain barrier
Bcl2	B-cell CLL/lymphoma 2
BCSFB	blood–cerebrospinal fluid barrier
BRE	brain and reproductive organ expressed gene
CER	cerebellum
CNS	central nervous system
CSF	cerebrospinal fluid
CTX	cortex
DD	death domain
DENN	differentially expressed in normal versus neoplastic
EAE	experimental allergic encephalomyelitis
FADD	Fas-associated death domain
HIP	Hippocampus
HIV	human immunodeficiency virus
MADD	mitogen-activated protein kinase-activating death domain
MCAO	middle cerebral artery occlusion
MDMA	3,4-methylenedioxymethamphetamine
METH	methamphetamine
MHC	major histocompatibility complex
MK-801	(+)-5-methyl-10,11-dihydro-5H-dibenzo [a,d]cyclohepten-5,10-imine maleate
MnSOD	manganese superoxide dismutase
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	multiple sclerosis

"The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health."

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NFκB	nuclear factor kappa B
NIK	nuclear factor kappa B inducing kinase
NMDA	*N*-methyl-D-aspartic acid
PD	Parkinson's disease
RIP	receptor-interacting protein
TACE	TNF-α converting enzyme
TNF	tumor necrosis factor
TNFR	tumor necrosis factor receptor
TNFR-DKO	tumor necrosis factor receptor double knockout
TRADD	TNF receptor-associated death domain
TRAF	TNF receptor-associated factor
TRIP	TRAF-interacting protein

Introduction

In the central nervous system (CNS), the proinflammatory cytokine TNF-α is considered the principal mediator of neuroinflammation that elicits a cascade of cellular events culminating in neuronal death. At the same time, TNF-α affords neuroprotection in certain neurological conditions. Thus, TNF-α appears to exhibit a dual role in the brain, and such effects appear to vary across brain areas, thereby, complicating the understanding of this double-edged cytokine. Here, we review from literature, the neurotoxic and neuroprotective roles of this proinflammatory cytokine, survey the regional selectivity of its action, and discuss the possible mechanisms by which TNF-α mediates its conflicting effects in the CNS.

Proinflammatory responses in the brain

Brain immune and inflammatory responses occur as a consequence of microglial activation. The magnitude of the neuroinflammatory response elicited depends on the spectrum of inflammatory mediators that are produced by neural cells in response to an insult. Cytokines, chemokines, prostaglandins, free radicals, pentraxins, complement components, anaphylotoxins, proteases, and adhesion molecules are among the several factors that mediate neuroinflammation (McGeer and McGeer 2004; Minghetti 2005). Neural injury can serve both as a cause and/or a consequence of cytokine or chemokine signaling. Cytokines are a family of low molecular weight, multifunctional pleiotrophic polypeptides that regulate cell activation, proliferation, and differentiation. Chemokines (chemoattractant cytokines) are low molecular weight (8–11 kDa) glycoproteins with potent leukocyte activation and chemotactic activity. In addition, they are known to play a role in cell cycle regulation and differentiation. Both cytokines and chemokines initiate and promulgate inflammatory reactions. The actions of such proinflammatory mediators contribute to manifestation of neurological (e.g., stroke), neurodegenerative (e.g., Parkinson's disease, Alzheimer's disease), infectious (e.g., HIV-1, bacterial or viral meningitis, cerebral malaria), autoimmune disease (e.g., multiple sclerosis) and chemically induced (MPTP, methamphetamine, kainic acid, 6-hydroxydopamine) neurotoxic conditions (Francis et al. 1995; Bruce et al. 1996; Seilhean et al. 1997; Munoz-Fernandez and Fresno 1998; Gartner and Liu 2002; Sriram et al. 2002a; McGeer and McGeer 2004; Minghetti 2005; Sriram et al. 2006a, b).

Sources of proinflammatory factors in the brain

The CNS has for long been regarded as an immune privileged organ, with the blood–brain barrier (BBB) tightly regulating the influx of immune cells and mediators from the vascular compartment to the brain parenchyma (Perry 1998). However, recent studies have shown that immune cells do migrate across the BBB and blood–cerebrospinal fluid barrier (BCSFB), albeit at very low levels, suggesting that immune surveillance can occur in the brain (Engelhardt 2006). Under normal physiological conditions, this immune cell entry is passive, due to the lack of antigenic presentation from major histocompatibility antigen (MHC) molecules. Furthermore, the unique CNS microenvironment regulates immune responses and migration of immune cells into the brain. However, under pathological conditions, immunocompetent cells can readily migrate across the endothelial BBB and epithelial BCSFB and enter the brain parenchyma.

This immune cell influx, during local infections and neuropathological event, is thought to be elicited by glial cells, especially the microglia. Mounting evidence indicate that microglia, in addition to their phagocytic function, gain antigen-presenting capabilities through expression of MHC components (Aloisi 2001; Carson et al. 2006). Microglia and astrocytes, the major glial cell types in the brain, become "activated" or "reactive" in response to diverse insults of the CNS (Table 1) and elicit a myriad of proinflammatory cytokines, chemokines, and trophic factors to render neural immunity (Raivich et al. 1996; Ransohoff et al. 1996; Stoll and Jander 1999). Microglia function as the microsensors of the brain and play an important role in detecting subtle changes in the neuronal microenvironment (Kreutzberg 1996). Both microglia and astrocytes express and release inflammatory mediators following brain injury, as seen in neurological and neurodegenerative disorders (Dickson et al. 1993; McGeer and McGeer 1998; Masliah and LiCastro 2000; Vila et al. 2001), and following experimental brain injury (Fan et al. 1996; Sriram et al. 2002a, 2006a, b).

Table 1 Neuronal injury is associated with glial activation

CNS disease or injury conditions associated with microglial and astroglial activation

Disease/injury condition	Brain area affected	Reference
Neurologic conditions		
Alzheimer's disease	Cerebellum, cortex	Wierzba-Bobrowicz et al. 2002
Alzheimer's disease	Cortex	Versijpt et al. 2003
Amyotrophic lateral sclerosis	Cortex, hippocampus	Wilson et al. 2001
Creutzfeldt-Jakob disease	Cerebellum, cortex	Gray et al. 1999
Creutzfeldt-Jakob disease	Cortex	Aoki et al. 1999
Multiple sclerosis	Cortex	Petzold et al. 2002
Parkinson's disease	Substantia nigra	Banati et al. 1998
Parkinson's disease	Substantia nigra	Hirsch et al. 2003
CNS Infections		
Bacterial infection (pneumococcal)	Hippocampus	Gianinazzi et al. 2003
Bacterial infection (streptococcal)	Cortex, hippocampus	Bogdan et al. 1997
Viral infection (dengue)	Cortex, hippocampus	Sanchez-Burgos et al. 2004
Viral infection (HIV)	Basal ganglia	Persidsky et al. 2001
Viral infection (HIV)	Cortex, basal ganglia	Seilhean et al. 1997
Viral infection (HIV)	Cortex, hippocampus	Vanzani et al. 2006
Viral infection (Measle)	Cortex, hippocampus	Manchester et al. 1999
Viral infection (Rabies)	Hippocampus, thalamus	Marquette et al. 1996
Brain injury		
Cerebellar stab injury	Cerebellum	Ajtai and Kalman 1998
Closed head injury	Brain wide	Engel et al. 1996
Cortical stab injury	Cortex	Krum et al. 2002
Cortical stab injury	Cortex	Isono et al. 2003
Facial nerve lesion	Cortex	Laskawi et al. 1997
Forebrain stab lesion	Hippocampus	Carbonell and Mandell 2003
Hippocampal stab wound	Hippocampus	Zhu et al. 2003
Mild focal brain ischemia	Striatum	Katchanov et al. 2003
Severe focal brain ischemia	Cortex	Cheung et al. 1999
Transient global ischemia	Hippocampus	Soltys et al. 2003
Transient MCAO	Substantia nigra	Dihne and Block 2001
Transient MCAO	Cortex, hippocampus	Butler et al. 2002
Toxic/chemical agents		
3-nitropropionic acid	Striatum	Teunissen et al. 2001
3-nitropropionic acid	Striatum	Ryu et al. 2003
6-hydroxydopamine	Striatum	Rodrigues et al. 2001
6-hydroxydopamine	Substantia nigra	Depino et al. 2003
Kainic acid	Hippocampus	Sriram et al. 2002b
Kainic acid	Hippocampus	Chung and Han 2003
Kainic acid	Hippocampus	Benkovic et al. 2004, 2006
Lipopolysaccharide	Substantia nigra	Arimoto and Bing 2003
MDMA	Striatum	Johnson et al. 2002
Methamphetamine	Striatum	Asanuma et al. 2003
Methamphetamine	Striatum	Sriram et al. 2002b, 2006b
Methamphetamine	Striatum	Thomas et al. 2004
MPTP	Striatum	Sriram et al. 2002a, 2006a, b
MPTP	Substantia nigra	Cardenas and Bolin 2003
MPTP	Substantia nigra	McGeer et al. 2003
Quinolinic acid	Striatum	Schiefer et al. 1998
Quinolinic acid	Striatum, Substantia nigra	Dihne et al. 2001
Rotenone	Striatum, Substantia nigra	Sherer et al. 2003
Trimethyltin	Hippocampus	Fiedorowicz et al. 2001
Trimethyltin	Hippocampus	Little et al. 2002

Evidence for *in vivo* microglial and astroglial activation, following disease, injury or exposure to chemical agents is presented.

Tumor necrosis factor (TNF)-α

TNF-α is synthesized as a 26-kDa membrane-bound polypeptide precursor that is cleaved by proteolysis to a 17-kDa subunit. The synthesis and secretion of TNF-α is regulated by TNF-α converting enzyme (TACE), a proteinase that is responsible for cleavage of TNF-α at the membrane surface. Upon cleavage, TNF-α is released as a bioactive homotrimer, which then exerts its effects in an autocrine and/or paracrine fashion. The biological actions of TNF-α are mediated through two distinct cell surface receptors, TNFR1 (p55) and TNFR2 (p75), to which it exhibits fairly equal affinity. Despite the fact that each TNF receptor mediates distinct cellular responses, there is considerable overlap of their signaling capabilities in mediating biological effects (Hsu et al. 1996; Declercq et al. 1998; Quintana et al. 2005). The differential patterns of localization of TNF receptors on neuronal or glial cells, their expression profile and activational state on these cells, and the down-stream effectors that they activate, are thought to play a critical role in determining if TNF-α will have a protective or cytotoxic role (Dopp et al. 1997, Sairanen et al. 2001, Fontaine et al. 2002; Dziewulska and Mossakowski 2003, Akassoglou et al. 2003). TNF receptors are members of the TNF superfamily and mediate signals via recruitment and inhibition of adapter proteins. Briefly, upon receptor activation, the adapter proteins, TNFR-associated death protein (TRADD) and differentially expressed normal versus neoplastic/MAPK activating death domain (DENN/MADD) bind to TNFR through the death domains (DD). Subsequently, Fas-associated death domain (FADD), receptor-interacting protein (RIP) and/or TNFR-associated factors (TRAFs) are recruited to promote physiological actions (see recent reviews, Aggarwal 2003; Hehlgans and Pfeffer 2005).

To delineate the beneficial and detrimental effects of TNF-α in the brain and to better understand its mechanisms of action, we review from literature the neurotoxic and neuroprotective roles of this proinflammatory cytokine and discuss the factors that may potentially influence its divergent actions.

Neurotoxic effects of TNF-α

TNF-α can be potently induced following brain injury and promote neuroinflammation and neurodegeneration. Elevated levels of this cytokine have been associated with the pathological effects of a variety of infectious, neurological, neurodegenerative, and neurotoxic conditions. Infectious diseases of the CNS are of bacterial or viral origin and affect the meninges (e.g., bacterial meningitis) or the parenchyma (e.g., viral encephalitis), respectively. Increased levels of TNF-α were detected in the CSF of patients with meningitis of bacterial but not viral origin. Elevated levels of TNF-α have been observed in the brain, cerebrospinal fluid (CSF), and serum of patients with Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and HIV-dementia, and following brain injury and chemical-induced neurotoxicity (see Table 2 for a listing of various studies documenting the neurotoxic effects of TNF-α).

In patients with AD, amyloid plaques characterized by in-filtered microglia were found to express high levels of TNF-α (Dickson et al. 1993; Eikelenboom et al. 2000). Late-onset AD is associated with three TNF polymorphisms: a-308 TNF promoter polymorphism, a-238 TNF promoter polymorphism, and a microsatellite TNF-α, which form a 2-1-2 haplotype (Collins et al. 2000). In experimental models of AD, β-amyloid triggers microglial activation and elicits the expression of TNF-α (Meda et al. 1995). Similarly, in a triple transgenic AD (3xTg-AD) mouse model, characterized by amyloid and neurofibrillary tangle deposition, neuroinflammatory responses occurred very early in the injury process, resulting in accumulation of TNF-α (Janelsins et al. 2005). These findings suggest the involvement of TNF-α-mediated inflammation in the pathogenesis of AD.

In patients with PD, significant increases in the expression of TNF-α have been reported in the caudate and putamen of postmortem brain samples (Boka et al. 1994; Mogi et al. 1994, Mogi et al. 1995). Unlike the association of TNF haplotype with late-onset AD, polymorphism of TNF gene in patients with PD has been associated with the early onset of the disease. The frequency of the −1031C allele, a high producer of TNF, increased significantly in early onset PD patients, suggesting a toxic role for TNF in PD (Nishimura et al. 2001). Increased expression of TNF-α has also been observed in several experimental models of PD (Mogi et al. 1999; Sriram et al. 2002a; Ferger et al. 2004; Sriram et al. 2006a, b).

TNF-α is implicated in the pathogenesis of MS. Increased levels of TNF-α protein were found in brain lesions, CSF, and serum of patients with MS (Hauser et al. 1990; Cannella and Raine 1995; Martino et al. 1997). In experimental allergic encephalomyelitis (EAE) animal models, increased TNF-α in the serum and CSF correlates with the peak symptoms (Villarroya et al. 1997).

In HIV-dementia, TNF-α is a predictor of neurotoxicity, and significant levels of this cytokine were found in the brains of HIV-seropositive patients with AIDS dementia, but not in non-demented patients (Wesselingh et al. 1993, Wesselingh et al. 1997). *Scid* mice inoculated with HIV-infected human macrophages develop HIV infection and express TNF-α (Tyor et al. 1993). Increased TNF-α expression in perivascular macrophages, microglia, and

endothelial cells was detected in midfrontal cortex, subcortical and deep white matter, and basal ganglia of patients with AIDS dementia complex (Seilhean et al. 1997). Recent comprehensive reviews discuss at length the role of TNF-α in HIV-dementia (Saha and Pahan 2003; Brabers and Nottet 2006).

In ischemic brain injury, TNF-α may play a critical role in the injury process. High levels of this cytokine have been reported in ischemic stroke models (Tarkowski et al. 1999, Vila et al. 2000; Intiso et al. 2004). In experimental models of ischemia, TNF-α was induced very early in the injury process and in a region-specific fashion (Liu et al. 1994; Saito et al. 1996). Saito et al. (1996) demonstrated that following transient global ischemia, TNF-α was selectively induced in the striatum and hippocampus but not in other brain areas. Furthermore, the expression of TNF-α following ischemic brain injury appeared to occur first in neurons, and a delayed expression of this cytokine was localized to glial cells (Meistrell et al. 1997; Buttini et al. 1996). Barone et al. (1997) have reported that following permanent middle cerebral artery occlusion (MCAO), the induction of TNF-α was associated with exacerbation of neurological deficits and infarct size, implicating this cytokine as a key player in ischemic brain injury.

TNF-α is also involved in traumatic brain injury. High levels of TNF-α have been reported in serum and CSF of patients with head injury (Goodman et al. 1990; Ross et al. 1994). In experimental models of traumatic brain injury, such as the fluid percussion injury (Taupin et al. 1993, Fan et al. 1996; Kita et al. 1997) and weight-drop contusion injury (Holmin et al. 1997), elevated levels of several cytokines including TNF-α were found. Similarly, in experimental closed head injury, activation of the complement component and increased expression of TNF-α has been reported (Shohami et al. 1994; Stahel et al. 2000).

Confirmation for the neurotoxic role of TNF-α comes from studies carried out to neutralize or antagonize the actions of TNF-α. Neutralizing antibodies against TNF-α were shown to be protective against cerebral ischemia (Lavine et al. 1998). Pretreatment with monoclonal antibodies to TNF-α reduced infarct volume and improved the neurological outcome. Similarly, neutralizing TNF-α activ-

Table 2 Evidence for a neurotoxic role of TNF-α: studies that suggest expression of TNF-α is harmful and initiates neurotoxicity and/or neurodegeneration

Evidence for a neurotoxic role of TNF-α

Disease/injury condition	Model	Species	Finding	Reference
Alzheimer's disease	–	Human	↑ TNF in plasma	Bruunsgaard et al. 1999
Alzheimer's disease	–	Human	TNF haplotype associated	Collins et al. 2000
HIV-dementia	–	Human	↑ TNF in cortex	Achim et al. 1993
HIV-dementia	–	Human	TNF polymorphism	Quasney et al. 2001
Multiple sclerosis	–	Human	↑ TNF in brain lesions	Cannella and Raine 1995
Multiple Sclerosis	–	Human	↑ TNF in CSF	Matusevicius et al. 1996
Parkinson's disease	–	Human	↑ TNF in CSF	Mogi et al. 1994
Parkinson's disease	–	Human	↑ TNF in serum	Dobbs et al. 1999
Parkinson's disease	–	Human	↑ TNF in substantia nigra	Boka et al. 1994
Parkinson's disease	–	Human	TNF polymorphism	Nishimura et al. 2001
Stroke	–	Human	↑ TNF in CSF, plasma	Vila et al. 2000
Stroke	–	Human	↑ TNF in serum	Intiso et al. 2004
Traumatic brain injury	–	Human	↑ TNF in CSF, serum	Shiozaki et al. 2005
Bacterial meningitis	Pneumococcal	Rat	↑ TNF in CSF	Gianinazzi et al. 2003
Bacterial meningitis	Pneumococcal	Rat	↑ TNF in hippocampus	Gerber et al. 2004
Bacterial meningitis	Streptococcal B	Rat	↑TNF in hippocampus, cortex	Bogdan et al. 1997
Dopaminergic neurotoxicity	METH	Mouse	↑ TNF in striatum	Sriram et al. 2006b
Dopaminergic neurotoxicity	METH	Rat	↑ TNF in frontal cortex	Flora et al. 2002
Excitotoxicity	Kainic acid	Rat	↑ TNF in hippocampus	de Bock et al. 1996
Head injury (diffuse axonal injury)	Fluid-percussion	Rat	↑ TNF in cortex, brain stem	Kita et al. 1997
Ischemia	Global	—	↑ TNF most brain areas	Sairanen et al. 2001
Ischemia	MCAO	Rat	↑ TNF in cortex	Botchkina et al. 1997
Multiple Sclerosis	EAE	Rat	↑ TNF in spinal cord	Villarroya et al. 1997
Parkinson's disease	6-OHDA	Rat	↑ TNF in striatum, nigra	Mogi et al. 1999
Parkinson's disease	MPTP	Mouse	↑ TNF in striatum	Sriram et al. 2002a, 2006a, b
Traumatic brain injury	Fluid-percussion	Rat	↑ TNF in cortex	Knoblach et al. 1999
Viral encephalopathy	Dengue 2 virus	Mouse	↑ TNF in hippocampus, cortex	Sanchez-Burgos et al. 2004
Viral infection	Rabies virus	Rat	↑ TNF in hippocampus, cortex	Marquette et al. 1996

ity with a recombinant type I soluble TNF receptor (TNF-binding protein, TNFbp), protected against microvascular perfusion impairment and ischemic injury induced by permanent MCAO (Dawson et al. 1996). Intrastriatal co-injections of TNFbp with *N*-methyl-D-aspartic acid (NMDA) reduced striatal injury, while intrahippocampal co-injections exacerbated excitotoxic damage (Galasso et al. 2000). Neutralizing soluble TNF with a dominant-negative TNF compound XENP345 was shown to protect against dopaminergic neurotoxicity (McCoy et al. 2006). XENP345, a PEGylated form of the TNF variant A145R/I97T, reduced retrograde nigral degeneration elicited by striatal injection of the dopaminergic neurotoxicant, 6-hydroxydopamine. Pharmacological intervention with MK-801, a noncompetitive NMDA receptor antagonist or dexamethasone was shown to exert neuroprotection against permanent MCAO. Both these agents blocked TNF-α production by 70% and reduced infarct size by nearly 50%, suggesting that despite their action at distinct cellular levels, these agents can modulate cerebral injury mediated by TNF-α. The immunosuppressant drug, FK506, is neuroprotective in experimental models of cerebral ischemia. FK506-mediated neuroprotection was shown to be associated with a selective decrease in the levels of TNF-α and IL-1β in glial cells. Thus, the mechanism of action of FK-506 seems to occur through modulation of glial response and inflammation (Zawadzka and Kaminska 2005). Pentoxifylline, a phosphodiesterase inhibitor and Dexanabinol (HU-211), a synthetic cannabinoid, have been shown to improve the outcome of experimental closed head injury mediated by TNF-α, especially when administered within the early time window of brain injury (Shohami et al. 1997). Similar to pentoxifylline, the specific type IV phosphodiesterase inhibitor rolipram, protected against striatal excitotoxic injury induced by quinolinic acid (Block et al. 2001). While anti-TNF strategies have been fairly successful in experimental models, their translation to clinical conditions has been hampered by high rate of severe side effects and/or failure to demonstrate significant survival benefit.

The mechanisms by which TNF-α appears to mediate its toxic effects (Skias et al. 1987; Benveniste et al. 1989; Shrikant et al. 1994; Chao and Hu 1994; Rosenberg et al. 1995; Probert and Selmaj 1997; Lucas et al. 1997; Koller 1997; Christov et al. 2004; Brabers and Nottet 2006) include (1) endothelial cell stimulation and alteration of blood–brain barrier integrity, thus, promoting immune cell adhesion and infiltration into the injured brain, (2) stimulation of apoptosis of brain microvascular endothelial cells, (3) activation of microglial cells, thereby, triggering a "vicious cycle" of oxidative outburst and inflammatory cytokine release, (4) modulation of the expression of MHC class components on neurons and astrocytes, thereby, rendering the astrocytes vulnerable to cytotoxic T-cells, (5) potentiation of glutamate-mediated toxicity by preventing glutamate uptake, (6) increase in vasogenic brain edema, (7) modulation of ion currents and intracellular calcium homeostasis, (8) regulation of membrane potential and long-term potentiation. Thus, TNF-α appears to be a central mediator of neuroinflammation and brain injury.

Neuroprotective effects of TNF-α

While several lines of evidence point towards a neurotoxic role for TNF-α in the CNS, this cytokine does not appear to be strictly neurotoxic. Besides its key role in maintaining CNS homeostasis, TNF-α is known to influence survival, differentiation, proliferation, and growth. These features highlight a potential protective role for this cytokine. Indeed, this cytokine has been shown to afford protection against brain injury (Table 3). TNF-α has been shown to promote reparative remyelination in an experimental model of demyelination (Plant et al. 2005). In this case, TNF-α appears to promote the survival of oligodendroglia, thereby, facilitating remyelination. TNF-α protects against the neuronal cell death induced by β-amyloid peptide (Barger et al. 1995; Goodman and Mattson 1996; Kaltschmidt et al. 1999). The protective mechanism was attributed to the role

Table 3 Evidence for a neurotrophic role of TNF-α: studies that suggest expression of TNF-α is beneficial and protects neurons against insults

Evidence for a neuroprotective role of TNF-α				
Disease/injury condition	Model	Cell/Brain area examined	Mechanism of protection	Reference
Alzheimer's disease	Aβ	HIP neurons	↑ NF-κB, Regulates Ca^{2+}	Barger et al. 1995
Alzheimer's disease	Aβ	HIP neurons	↑ NF-κB, ↑MnSOD	Mattson et al. 1997
Alzheimer's disease	Aβ	CER neurons	↑ NF-κB	Kaltschmidt et al. 1999
Alzheimer's disease	Aβ	Human neuronal cells	↑ Bcl-2	Tarkowski et al. 1999
Alzheimer's disease	Aβ	SH-SY5Y cells	↑ NF-κB, ↑ MnSOD	Sompol et al. 2006
Excitotoxicity	Glutamate	HIP neurons	Ceramide→ antioxidant defense	Goodman and Mattson 1996
Excitotoxicity	NMDA	CTX & HIP neurons	Regulates Ca^{2+}	Cheng et al. 1994
Excitotoxicity	NMDA	CTX neurons	↑ K^+ A-current density	Houzen et al. 1997

of TNF-α in regulating peroxide formation, calcium accumulation, activation of NF-κB, and antioxidant pathways. In another study (Houzen et al. 1997), cerebral cortical neurons were protected against NMDA-induced neurotoxicity by TNF-mediated mechanisms. Here, TNF-α regulated the voltage-gated membrane currents, particularly the outward potassium current density (A-current). Thus, an increase of A-current density induced by TNF-α contributed to neuroprotection.

Preconditioning with TNF-α also appears to be neuroprotective in ischemic cerebral injury. Intracisternal administration of TNF-α significantly reduced infarct size and decreased microglial activation in a MCAO model of cerebral ischemia (Nawashiro et al. 1997). TNF-α-induced preconditioning mediated through ceramide, protected neurons against ischemic injury (Ginis et al. 2002). These findings suggest that TNF-α is involved in development of ischemic tolerance.

TNF-α plays a neuroprotective role against excitotoxic injury in the hippocampus (Cheng et al. 1994; Bruce et al. 1996; Gary et al. 1998). Excitotoxic death of cortical neurons mediated by NMDA was abolished by TNF-α (Carlson et al. 1998). Co-injections of TNF-α and NMDA into the hippocampus reduced excitotoxic injury; however, intrastriatal co-injections did not alter the severity of injury (Liu et al. 1999). TNF-α also mediates neuroprotection in response to acute nitric oxide excitotoxicity (Turrin and Rivest 2006). Whereas elevated levels of TNF-α are associated with neuroprotection against excitotoxic damage in hippocampus, a lack of enhanced expression of TNF-α in hippocampus is associated with significant chemically induced damage to this structure (Little et al. 2002).

The emergence of knockout and transgenic technologies has revolutionized the approach towards understanding the functional role of genes. In this regard, the availability of transgenic mice lacking TNF, TNFR1, or TNFR2 genes has greatly facilitated research towards understanding the role of this proinflammatory cytokine in the brain. Mice deficient in both TNF receptors were found to be more susceptible to hippocampal excitotoxic and ischemic injury (Bruce et al. 1996; Gary et al. 1998). Similarly, exacerbation of damage and altered NF-κB activation was observed in TNF-deficient mice after traumatic brain injury (Sullivan et al. 1999). Mice lacking TNF receptors exhibited increased oxidative stress and striatal lesion size following 3-nitropropionic acid (3-NP) administration (Bruce-Keller et al. 1999). On the other hand, we have previously shown that mice lacking both TNF receptors, but not individual receptors, were protected against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; Sriram et al. 2002a). These paradoxical findings suggested that TNF-α was capable of mediating differential effects in specific brain areas. Indeed, we recently demonstrated that TNF-α plays a region-specific role in the brain (Sriram et al. 2006a). While deficiency of TNF receptors blocked MPTP neurotoxicity in the striatum, the lack of these receptors rendered the hippocampus, an otherwise nontarget region for MPTP effects, vulnerable to injury. Thus, TNF-α serves to promote neurodegeneration in striatum, while affording protection against neurodegeneration in the hippocampus (Fig. 1, depicts the region-specific actions of TNF-α in a neurotoxic/neurodegenerative scenario). While knockout and transgenic technologies aid understanding of the gene function, there is limited knowledge of compensatory mechanisms associated with genetically modified animals. More recent approaches such as conditional knockouts and manipulation of genes via inducible promoters may perhaps provide a better understanding of the gene function in the future.

The mechanisms by which TNF-α appears to mediate its neuroprotective effects (Grassi et al. 1994; Barger et al. 1995; Mattson et al. 1995; Bizette et al. 1996; Goodman and Mattson 1996) include (1) activation of astroglia and stimulating neurotrophic factor release, (2) activation of repair processes of peripheral nerves and cerebral microvasculature, (3) stimulation of synaptic currents and thereby mediating neuronal plasticity, (4) activation of NF-κB pathway, (5) induction of anti-apoptotic factors such as Bcl-2, (6) ceramide-mediated induction of antioxidant defense pathways, (7) regulation of extracellular calcium and the calcium binding protein calbindin-D28K.

Factors influencing the divergent actions of TNF-α

Based on the extensive evidence reviewed above in relation to the neurotoxic and neuroprotective roles for TNF-α, sufficient data exist to indicate that this cytokine has paradoxical functions that can result in simultaneous stimulation of cell survival and death pathways. How the balance between these divergent roles is maintained determines the ultimate role for this cytokine.

While basal physiological levels of TNF-α are not necessarily indicative of a neuroprotective versus a neurotoxic function (Cheng et al. 1994; Mattson et al. 1995; Uno et al. 1997), differences in the levels and activational state of the TNF receptors and related downstream effectors may serve to confer differences in its role. The type 1 (TNFR1, p55) and type 2 (TNFR2, p75) TNF receptors are members of the TNF receptor superfamily, which includes other prominent receptors like Fas, lymphotoxin β receptor, p75 nerve growth factor receptor, and CD40, among others. These receptors share substantial homology, but function in a mechanistically diverse fashion (Sprang 1990, Tartaglia et al. 1991). Constitutive expression of TNF receptors is reported to occur in neurons and blood vessels; however, these receptors are expressed on glial cells (microglia and

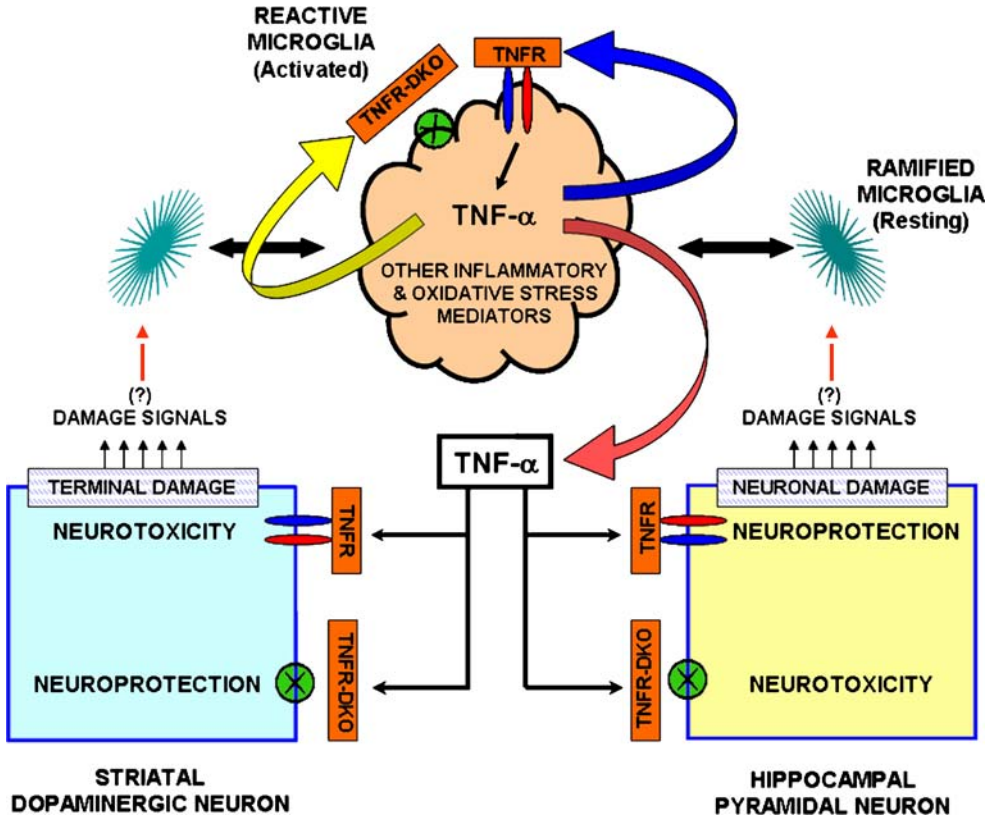

Fig. 1. Schematic diagram depicting a region-specific role for TNF-α in the brain: neuronal injury is associated with release of "mysterious injury factors" that activate microglia and/or astroglia. There is heterogeneity in the distribution, morphology, and activation of microglia across brain areas. Striatal dopaminergic neurotoxicity is associated with microglial activation and elaboration of microglia-derived cytokines like TNF-α. TNF-α elicits dopaminergic nerve terminal degeneration by signaling through the TNF receptors localized on dopaminergic nerve terminals. Deficiency of TNF receptors suppresses microglial activation, and as a consequence, the dopaminergic neurotoxicity. Paradoxically, lack of TNF receptors renders the hippocampus vulnerable to neuronal degeneration. Thus, TNF-α plays a dual role in brain: neurotoxic in the striatum and neurotrophic in the hippocampus.

astroglia) and macrophages following brain injury. While TNFR2 appears to be predominantly expressed by macrophages, microglia exhibit a differential pattern of immunostaining for both TNF receptors (Dziewulska and Mossakowski 2003). Thus, the differential patterns of expression of TNF receptors on neuronal and glial cells are thought to play a critical role in determining if TNF-α will have a protective or cytotoxic role (Dopp et al. 1997, Sairanen et al. 2001, Fontaine et al. 2002; Dziewulska and Mossakowski 2003, Akassoglou et al. 2003). Upon activation, the TNF receptors interact with an array of intracellular adapter proteins to mediate downstream cell signaling. TNFR1 associates with TRADD, a death domain protein that transduces signals through FADD and FADD-like interleukin-1beta-converting enzyme (FLICE), and activates intracellular proteases of the caspase family. TNFR1 and TNFR2 also associate with TRAFs, which mediate activation of the nuclear factor kappa B (NF-κB) family of transcription factors. Specifically, TRAF2 mediates NF-κB activation via NF-κB inducing kinase (NIK), which leads to IκB degradation and release of NF-κB. Activation of NF-κB promotes gene expression that can elicit either neurotoxic or neuroprotective effects. Evidence for this dual role comes from studies that show that TNF-α-mediated induction of NF-κB is associated with neuronal survival (Barger et al. 1995; Kaltschmidt et al. 1999; Albensi and Mattson 2000) or the inability of TNF-α to induce NF-κB is associated with increased neurotoxicity (Botchkina et al. 1999; Sriram et al. 2006a). One possible reason for the diverse role exhibited by TNF-α could be attributed to the differences in the activation of NF-κB, which is tightly regulated at the level of TRAF2. Three regulatory proteins (TRAF-interacting proteins), I-TRAF, TRIP, and A20, bind to TRAF2 and inhibit its ability to activate NF-κB. In addition to regulation of NF-κB by TRAF2, in the brain, NF-κB is also regulated by a novel stress response gene, brain, and reproductive organ expressed (BRE). BRE appears to be activated specifically by TNFR1 and inhibits NF-κB activation (Gu et al. 1998). Thus, the efficiency of NF-κB activation in neuronal and/or glial cells depends on the duration of NF-κB activation and the differential activity of the regulatory proteins, which eventually determine the neurotoxic or neurotrophic outcome elicited by TNF-α. Indeed, such differences in the expression of NF-κB have been known to occur in the CNS (Joseph et al. 1996; Galasso et al. 2000). TNF-α is a key player in the pathogenesis of dopaminergic neurodegeneration and is up-regulated in the striatum following MPTP and methamphetamine (Sriram et al. 2002a, Sriram et al. 2006a, b). Despite an early and large increase in the striatal expression of TNF-α, activation of NF-κB was not detectable. These findings were consistent with an earlier observation (Teismann et al. 2001) and suggest that the lack of NF-κB activation may result in increased neurotoxicity

(Botchkina et al. 1999). Thus, TNF-α elicits a neurotoxic response in the striatum. Conversely, activation of NF-κB by TNF-α in the hippocampus was neuroprotective (Tamatani et al. 1999). From these findings, a multifarious identity emerges for TNF-α that is influenced not only by regulation of TNF signaling, but also by regional differences in its cellular expression across brain regions.

In the brain, TNF-α is predominantly produced by microglia. Microglia are localized in the vicinity of neurons and play an important role in host defense, sharing many phenotypic features with hematogenic macrophages. As the primary immune cell in the CNS, they play a dual role in cellular responses to neuronal injury: a pathogenic role that initiates inflammation and exacerbates degeneration and a neuroprotective role (Stoll and Jander 1999; Gonzalez-Scarano and Baltuch 1999; Streit et al. 1999). Under normal physiological environment, microglia reside in a quiescent state exhibiting a ramified morphology (ramified or resting microglia). In response to local injury, the ramified microglia retract their processes and acquire an amoeboid (activated microglia) or rounded (phagocytic microglia) shape. Reactive microglia express several immunological surface proteins, such as, complement type receptors (e.g., OX-42), major histocompatibility complex class II antigens (e.g., OX-6), and cytoplasmic/lysosomal antigens (e.g., ED-1, ED-2). The expression of these markers differs based on the type and extent of injury and their topographical distribution in the brain. Although microglia are abundant in the brain, the distribution and morphological heterogeneity of these cells vary across brain regions (Lawson et al. 1990). The hippocampus, basal ganglia, and substantia nigra are densely populated with microglia; moderate levels are found in cortex, thalamus, and hypothalamus, while less dense areas include the cerebellum and brain stem. The morphology of the microglia varies with their distribution, and they appear as (1) round with thick and short processes, typically localized in areas devoid of blood brain barrier, (2) longitudinally branched, as seen in fiber tracts, and (3) radially branched, distributed throughout the neuropil. Thus, the susceptibility of various brain regions to neurotoxic insults may be attributed to regional differences in microglial distribution and number, the microglial phenotype (morphology), and the repertoire of proinflammatory cytokines and chemokines they express. Marked differences in the regional expression of microglia-derived cytokines are apparent. The basal expression of proinflammatory mediators, TNF-α, MCP-1, and IL-1α were significantly higher in the hippocampus compared to striatum (Ren et al. 1999; Sriram et al. 2006a). Such regional variations in microglial distribution, morphology, and gene expression, influence cross talk with their immediate neuro-astroglial microenvironment, their response to external stimuli, and the timing and threshold of TNF-α release. A combination of these interactions ultimately define a neurotoxic or neurotrophic role for this cytokine.

One implication of such regional selectivity and dual role for microglia-derived TNF-α in the brain is that anti-TNF therapies currently in practice to treat certain auto-immune and inflammatory conditions may have negative consequences on the nervous system. It is therefore critical that a comprehensive screening of anti-TNF therapies across brain regions is performed to determine any adverse effects and evaluate the efficacy of such treatments. Overall, one has to demonstrate caution in extrapolating the results of preclinical anti-TNF studies into clinical practice.

Summary

Neurotoxicity and neurodegeneration are consequences of a shift in the subtle balance between neuronal survival and death, which is mediated by proinflammatory cytokines such as TNF-α. Enhanced expression of TNF-α can be observed in a variety of brain insults in association with other neuroinflammatory processes. Simultaneously, TNF-α possesses the ability to activate neuroprotective mechanisms. Thus, a double-edged role for this cytokine in the CNS has been documented. In reviewing the literature, a multifarious identity emerges for TNF-α that is influenced not only by the signaling pathways it activates, but also by regional differences in microglial distribution and morphology, the cells that predominantly produce this cytokine. Thus, the extent of microglial activation in specific brain regions, the timing and threshold of TNF-α expression, and the conditions that stimulate regulation of TNF signaling, eventually determine whether TNF-α plays a neurotoxic or neurotrophic role in the CNS.

Emerging concepts

Although it remains a relatively unexplored research arena, glial activation biology and drug–immune interactions may contribute to adverse neural outcomes associated with self-administration of drugs of abuse and the progression of HIV infection (Berman et al. 2006). In this context, drugs of abuse can encompass compounds as diverse as opioids and amphetamines. Methamphetamine and the HIV-1 protein Tat interact to exacerbate dopaminergic neurotoxicity (Theodore et al. 2006). It is suggested that Tat-induced expression of TNF-α may predispose striatal dopaminergic nerve terminals to subsequent damage by methamphetamine. Altered immune responses reflect stimulation of innate immune responses following the loss of adaptive immune response (Berman et al. 2006). Glial activation events that reflect stimulation of innate immunity can

involve microglia and astrocytes at known targets of a given drug of abuse, e.g., the basal ganglia, but more generally, may reflect alterations at the BBB that effect enhanced entry of peripheral immune components into the brain parenchyma. Chief among proinflammatory mediators implicated in these adverse effects of drug abuse is TNF-α (see Thomas and Kuhn 2005; Sriram et al. 2006b). Of course, many other immune and nonimmune effectors may play a role in chronic adverse outcomes associated with drug abuse, but it is becoming clear that drug–neuron–glial–immune interactions up- and downstream of TNF-α are involved.

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