ROLE OF CYTOKINES IN NEURODEGENERATIVE DISEASES

Shubha Niranjan*, Pramod Kumar Sharma, Vipin Kumar Garg, Sambhu Charan Mondal, Avnesh Kumar Singh

Department of Pharmaceutical Technology, Meerut Institute of Engineering and Technology, Baghpat Bypass Crossing, NH-58, Meerut-250005, Uttar Pradesh, India.

ABSTRACT

Cytokines which were earlier known as immune cell mediators in the periphery has been found to be involved in the alteration of several neurological functions and dysfunctions. These may originate from the peripheral immune organs and cross blood brain barrier or produced from glial cells. They have been implicated in various neurodegenerative diseases such as Parkinsonism, Alzheimer, Amyotrophic lateral sclerosis, Friedreich’s ataxia etc. Both direct and indirect evidences were suggested for involvement of cytokines in neurodegeneration and neurotoxicity. Cytokine receptors include immunoglobulin super family (IL-1 type), Interferon (type-2) family, TNF (CD40, CD27 and CD30) family and G-protein coupled receptors. These are known to be involved in modulation of several neurological functions through Janus-Kinase-Signal transducer and activator of transcription (JAK-STAT) signalling pathway. Cytokines interaction with glutamatergic system plays essential role in cytokine-induced neurodegeneration. Cytokine activities have been delineated in-vitro using recombinant cytokines and purified cell populations, or in-vivo with knock-out mice for individual cytokine genes. Elevated TNF levels in brain and CSF were found in parkinsonian patients which can be attributed the possible basis of neurodegeneration. Similarly, in Alzheimer’s patient’s expression of various pro-inflammatory mediators including TNF-α, IL-1β, IL-6 has been shown to be closely associated with β A4 plaques.

Keywords: Cytokines, Interleukins, Immunoglobulin, Glutamatergic system, βA4 plaques.

INTRODUCTION

Cytokines are chemical molecules secreted by cells into the extracellular fluid which can function as autocrine, paracrine or endocrine hormone. These are the multifunctional molecules which can mediate interactions between various cells.[1] There are three main mechanisms of neuronal cell death which may act in-association/combination or separately to cause neurodegeneration. This triplet of excitotoxicity, metabolic compromise and oxidative stress causes neuronal cell death that are both necrotic and apoptotic in nature. Each of these three mechanisms is believed to
play a role in the neurodegeneration that occurs in neurodegenerative disorders such as Parkinson’s and Huntington’s diseases. Neurodegeneration is the term for excessive loss of structure and function of neurons, and may also causes death of neurons. Many neurodegenerative disorders occur as a result of degeneration of neurons. As research on sub-cellular level progresses, many similarities appear which relate these diseases to one another. These similarities offer hope for therapeutic advances that could abate many such diseases\cite{2-3}. Cytokines which were earlier known as immune cell mediators in the periphery has been found to be involved in the alteration of several neurological functions and dysfunctions. These may originate from the peripheral immune organs and cross blood-brain barrier or produced from glial cells. Both direct and indirect evidences were suggested for involvement of cytokines in neurodegeneration and neurotoxicity.

**Role of cytokines in neurodegenerative disorders**

Recent findings on Cytokines which were earlier described as immune cell mediators in the periphery suggest their involvement in the modulation of several neurological functions and dysfunctions. These molecules may be involved in the communication of systemic injury to the brain, mediation of physiological sleep, infection and inflammation, alteration of the responses to peripheral nerve injury, control of behaviour, synaptic plasticity and in the progression/inhibition of neurodegeneration. Cytokines have been implicated as mediators and inhibitors of various forms of neurodegeneration. Their release is induced in response to brain injury and these are found to possess diverse actions that in turn can cause, exacerbate, mediate and/or inhibit cellular injury and repair.\cite{4}

The evidences for the contribution of cytokines to acute neurodegeneration focuses primarily on Interleukin (IL-1), transforming growth factor-α (TNFα) and transforming growth factor-β (TGFβ). The Primary action of TGFβ is neuroprotection, while TNFα may be found to cause neuronal injury in addition to the protective function. IL-1 mediates ischemic, excitotoxic and traumatic brain injury through its multiple actions on glia and neurons.\cite{5}

Recognising the role of cytokine action in acute neurodegeneration could lead to novel and effective therapeutic strategies, some of which are already in clinical trials. The numerous cytokines affecting the central nervous system may have two possible origins:
(i) the peripheral immune organs which cross the blood-brain barrier and (ii) the glial
cells such as astrocytes and microglia and certain neurons.

Common pathways of neuronal cell death are:
1. Disruption of ion homeostasis, particularly intracellular calcium (Ca$^{2+}$) increase.
2. Excessive neuronal activation.
3. Impairment of classical neurotransmitter systems.
4. Production of neurotoxic mediators such as nitric oxide and reactive oxygen species.
5. Activation of genes that trigger the apoptotic pathway.

Prion infections in the central nervous system are characterised by reactive gliosis
followed by ensuing degeneration of neuronal tissue. The activation of glial cells, which
precedes neuronal death, is thought to be caused by the deposition of misfolded
proteinase K-resistant, isoforms (termed PrP$^{res}$) of the prion protein (PrP) in the brain.
Cytokines and chemokines released by PrP$^{res}$-activated glia cells may directly or
indirectly accord the disease development by augmentation and induction of the neuronal
gliosis and cytotoxicity.$^{[6]}$

The process of inflammation via inflammatory mediators such as cytokines in
Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis has recently
come under increased scrutiny. Associated with these inflammatory responses are one of
the cytokine named TNF-α and reactive oxygen species (ROS). Both of these are
believed to be derived from brain microglia.$^{[7]}$ The antibody-mediated immune responses,
of microglial cells and of certain cytokines e.g. interleukin-1, plays significantly important
role in excitotoxic neural degeneration.$^{[8]}$ Cytokines, (particularly interleukins and growth
factors) are synthesized in the brain and induced by brain damage. IL-1 appears to be
directly involved in conciliating ischemic and excitotoxic brain damage, whereas growth
factors (e.g., bFGF, NGF), and the phospholipids binding protein lipocortin-1 is thought
to exhibit neuroprotective actions. Recombinant IL-1 receptor antagonist administration
markedly abates the damage produced by cerebral ischemia or activation of N-Methyl-D-
aspartate (NMDA) receptors in the rat brain. The mechanism of action of these cytokines
on neurodegeneration is not completely explored, but indirect evidence has insinuated the
significant role of corticotrophin releasing factor, arachidonic acid, and nitric oxide (NO).
In vitro administration of interleukin-1, growth factors and lipocortin-1 produces effects
that are found to have an eloquent effect on intracellular calcium homeostasis, which is important in neurodegeneration. Pharmacological intonation of the expression and/or actions of cytokines in the brain can be of considerable therapeutic advantage in the treatment of acute neurodegeneration.\[9\]

**Interactions of Cytokines with the glutamatergic system**

Among the different mechanisms possibly involved in cytokine-induced neurodegeneration, cytokines interaction with the glutamatergic system is of great importance. Several pathological conditions are dependent on disproportionate glutamate release and subsequent over stimulation of the NMDA receptor; this suggests that there is some complementary functional interaction between IL-1 and NMDA receptors. Further studies revealed that intracerebral injection of NMDA in perinatal rat brain stimulates the production of IL-15 and in adult rat brain IL-1 exacerbates the neuronal damage, also the intra-hippocampus injection of IL-1 is found to induce proconvulsant actions in rats that can be blocked by selective antagonism of NMDA receptors.

**Role of Cytokines in Parkinson's disease (PD)**

PD is a movement disorder provoked by degeneration of the nigrostriatal dopamine neurons in the substantia nigra pars compacta and the resultant scarcity in the neurotransmitter- dopamine at the nerve terminals in the striatum region of brain. Higher levels of pro-inflammatory cytokines are found in brains of Parkinsonian patient’s and inflammation has been suggested as the major contributor of the underlying neurodegeneration. Studies have proclaimed the presence of increased levels of pro-inflammatory cytokines such as TNF-α, IL-1, IL-6 and decreased levels of neurotrophins such as brain-derived neurotrophic factor (BDNF) in the nigrostriatal region of postmortem brains and/or in the ventricular or lumbar cerebrospinal fluid (CSF) in patients with PD, in animal models such as 4-methyl-4-phenyltetrahydro pyridine (MPTP) and 6-hydroxydopamine (6-OHDA)-induced PD. These changes in Cytokine and neurotrophin levels may be triggered by activated microglia, which may then boost apoptotic cell death and can cause subsequent phagocytosis of dopaminergic neurons. During the inflammatory process, proinflammatory cytokines released by microglia act on the endothelium of blood–brain barrier (BBB) cells to provoke up regulation of adhesion molecules. This up regulation then leads to the recruitment of T cells and
monocytes which then release more cytokines.\textsuperscript{[10]} Cytokines act as pleiotropic factors which may promote signals that lead to cell death or exert neuroprotective effects. As a result, microglial cells may regulate cellular changes that can cause harm or benefit by producing cytokines or neurotrophins. Inflammatory cytokines (TNFα, IL-1β and interferon γ) are important mediators of inflammation in PD. They may mediate neurotoxicity by two mechanisms:

1. Direct mechanism- through receptor binding on dopaminergic neurons or
2. Indirect mechanism- through glial-cell activation and expression of inflammatory factors. Like TNFα, these pro-inflammatory cytokines might activate cell surface receptors expressed on dopaminergic neurons that are coupled to proapoptotic cell death pathway.\textsuperscript{[11]}

**Mechanisms of neuroinflammatory processes in Parkinson’s disease**

![Figure 1](image.png)

*Figure 1: Neuro-inflammatory process in Parkinson’s Disease*
Activated microglial cells might contribute to dopaminergic cell death by releasing cytotoxic inflammatory compounds such as pro-inflammatory cytokines like TNFα, IL-1β, and IFN-γ. Among other cytokines, TNFα may directly damage dopaminergic neurons by activating an intracellular death pathway coupled with TNF receptor. Pathways transduced by activation of TNF receptor 1 are linked to the induced expression of cyclooxygenase COX2 within the dopaminergic neurons. However, within microglial, astrocytic cells these cytokines might also stimulate the expression of inducible nitric oxide synthase (iNOS) through the expression and activation of the low-affinity receptor of immunoglobulin E (CD23). Further, this process might lead to the production of toxic amounts of NO free radicals. These free radicals could in-turn potentiate the expression & release of TNFα by adjacent microglial cells, thereby amplifying the inflammatory reaction. The microglial-dependent inflammatory reaction might contribute to the recruitment of activated CD4-T cells near dopaminergic neurons in the brain. These T cells might express and release several inflammatory factors such as TNFα, interferon γ and Fas ligand. Lymphocyte-derived Fas ligand mediates T cell-induced dopaminergic neuronal injury. Ligand-derived CD4-T cells might have a deleterious effect on dopaminergic neurons by me direct (by activating an intracellular death pathway coupled with Fas receptor expressed on the cell surface of dopaminergic neurons) or indirect (by activating Fas receptor expressed on activated microglial and reactive astrocytic glial cells) means, thereby stimulating their activation and the release of additional inflammatory factors. Figure 1: Neuroinflammatory process in PD. 

Role of cytokines in Alzheimer’s disease (AD)

Cytokines play a critical role in the development and progression of AD. In addition to astrocytes and microglia neurons themselves may aggravate inflammatory reactions in their proximity and so can accord their own destruction in AD. For example, neurons capable of producing inflammatory mediators. These include complement cyclooxygenase (COX), pro-inflammatory cytokines, the IL-6 receptor signal transducing component group M-CSF and others. Virtually all of these mediators have pro-inflammatory roles that could foment neurodegeneration and their levels are found to increase in the AD brain. Cytokines and chemokines presumably sub serve similar intracellular and intercellular signalling functions in microglia and astrocytes as they do...
in the periphery, although novel mechanisms have been proposed in the CNS for cytokines and chemokines. Virtually most of the cytokines and chemokines that have been reviewed in AD, especially the major pro-inflammatory mediators such as IL-1, IL-6, IL-8, TNFα, transforming growth factor-β (TGF-β) and macrophage inflammatory protein-1α (MIP-1α) are found to be upregulated in AD. A variety of inflammatory proteins has been identified in the postmortem brains of patients with AD. There are now enough evidences that in AD the deposition of amyloid-β (Aβ) protein presages a variety of events that ultimately leads to a local inflammatory response in brain. Elevated serum cytokines have been registered in neurological disorders: cerebral ischemia, epilepsy, brain trauma, multiple sclerosis, Creutzfeldt–Jakob disease, amyotrophic lateral sclerosis, AD and PD. However, the exact role in the path physiology of neurological disorders is not clear. Copper possess the ability to accept and donate electrons under physiological conditions hence, may act as a co-factor for a variety of enzymes such as cytochrome c oxidase. It is also required by immune cells for stress-induced release of fibroblast growth factor 1 and interleukin (IL)-1α and cytokines such as transforming growth factor (TGF)-β, tumour necrosis factor-α and IL-1β. Serum levels of TNF-α (P < 0.001), IFN-γ (P = 0.005), IL-6 (P < 0.001) were elevated in patients with WD, and this difference was found to be statistically significant when compared with control. There was an insignificant difference in serum IL-4 (P = 0.49) and IL-2 (P = 0.11) levels when compared with controls.

Mechanism of inflammatory process in Alzheimer’s disease

Key pathological signs in Alzheimer’s are generation and deposition of neurotoxic amyloid β peptides along with neurofibrillary tangle formation. Recent evidences suggest that the inflammation associated with this may be a third important component which if initiated once in response to neurodegeneration/dysfunction, may contribute to disease progression and/or chronicity. Various neuroinflammatory mediators such as complement activators and inhibitors, cytokines, radical oxygen species, chemokines and some inflammatory enzyme systems are expressed and released by astrocytes, microglia and neurons in the AD brain. Degeneration of aminergic brain stem nuclei including the locus ceruleus and the nucleus basalis of Meynert may facilitate the occurrence of inflammation in the projection areas. While inflammation has been
thought to arise secondary to degeneration, recent experiments have proclaimed that the inflammatory mediators may stimulate amyloid precursor protein processing by various means and then can establish an atrocious cycle. Notwithstanding the fact that some facets of inflammation may even be protective for by-stander neurons, anti-inflammatory treatment strategies should therefore need to be considered. Non-steroidal anti-inflammatory drugs have been shown to reduce the risk and delay the onset of development of AD. While, the precise molecular mechanism underlying this effect is still unknown, a number of possible mechanisms including cyclooxygenase 2 or gamma-secretase inhibition and activation of the peroxisome proliferator activated receptor gamma may alone or, more likely, in combination account for the epidemiologically observed protection.\[21\]

CONCLUSION

A significant number of the identified cytokines have been implicated in either the progression or treatment of neurodegenerative diseases. More recently, the complete sequencing of the human genome has led to the identification of additional cytokine homologues that presumably plays an important role in regulating the immune system. Many of these cytokines can be produced as recombinant proteins, and such cytokines can be administered systemically for regulation of immune response. Understanding the role of cytokine action in acute neurodegeneration could lead to novel and effective therapeutic strategies, some of which are already in clinical trials. Pharmacological modulation of the expression and/or actions of cytokines in the brain may be of considerable therapeutic benefit in the treatment of acute neurodegeneration. These findings offer hope for therapeutic advances that could abate many such diseases.

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For Correspondence:
Shubha Niranjan
Email: shubha.niranjan@gmail.com