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A REVIEW ON MOLECULAR MECHANISM OF NEUROINFLAMMATION DISEASE

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ABSTRACT

The inflammatory response in the brain associated with most chronic neurodegenerative diseases is termed neuroinflammation. Neuropathological and neuroradiological studies indicate that in certain neurodegenerative disorders neuroinflammation may be detectable years before significant loss of neurons occurs. The evidence from human studies and experimental models that implicate neuroinflammatory processes in the progressive neurodegeneration of the nigrostriatal pathway, the hallmark of Parkinson's Disease (PD). The neurotoxic role of microglia-derived inflammatory mediators which are suspected to hasten the death of nigral dopaminergic neurons, in particular the proinflammatory cytokine Tumor Necrosis Factor (TNF) and its downstream signaling pathways. The possibility that chronic microglia activation links proteinopathies to neurodegeneration.

KEYWORD: Neuroinflammation, Cytokines, Chemokines, Proteases, Amyloid precursor protein.

1. INTRODUCTION

1.1Neuroinflammation

Inflammation is the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells or irritants. Its a protective mechanism of cell attempt by the organism to remove the injurious stimuli as well as initiate the healing process for tissue. The inflammatory reaction is essential for preventing infection of the injured area as well as for initiating the process of healing. There are two type of inflammation i.e acute inflammation and chronic inflammation.

Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus. The acronym that may be used for this is "PRISH" for Pain, Redness, Immobility (loss of function), Swelling and Heat. The process of acute inflammation is initiated by cells already present in all tissues, mainly resident macrophages, dendritic cells, histiocytes, Kupffer cells and mastocytes Vasodilation and its resulting increased blood flow causes the redness (rubor) and increased heat (calor). Increased permeability of the blood vessels results in an exudation (leakage) of plasma proteins and fluid into the tissue (edema), which manifests itself as swelling (tumor).

Some of the released mediators such as bradykinin increase the sensitivity to pain (hyperalgesia, dolor). The mediator molecules also alter the blood vessels to permit the migration of leukocytes, mainly neutrophils and macrophages, outside of the blood vessels (extravasation) into the tissue. The neutrophils migrate along a chemotactic gradient created by the local cells to reach the site of injury.[1] The loss of function (functio laesa) is probably the result of a neurological reflex in response to pain.

There are five cardinal signs of inflammation were following……

1. **Rubor:** The redness that occur as a result of the increased blood flow to the inflamed area.

2. **Tumor:** Swelling of the inflamed tissue as a result of increased capillary permeability and fluid accumulation.

3. **Calor:** The increase in temperature (heat) that occur in the inflamed area as a result of increase blood flow.

4. **Dolor:** Pain that occur in the inflamed area as a result of stimulation of sensory neurons.

5. **Functio laesa:** Alteration or loss of function in the inflamed tissue.

A major pathogenic component in most neurological diseases: multiple sclerosis, Alzheimer disease, stroke, HIV dementia, brain tumors and several peripheral neuropathies. Involves both the central and peripheral nervous systems; bothsystems are comparatively encased in a protective barrier. Caused by both adaptive and innate immune mechanisms although innate immunity predominates.

Neuroinflammation represents the coordinated cellular response to tissue damage. Uncontrolled neuroinflammation can induce secondary injury.[2,3] Microglia display a dynamic and active phenotype with ongoing retraction and extension of processes into the brain parenchyma .[4] In the human brain, microglial activation and neuroinflammation have been associated with viral or bacterial infection, autoimmune disease such as multiple sclerosis, head trauma, vascular system damage, neuropsychiatric disorders, and neurodegenerative diseases.[5]

1.2 Causes of Neuroinflammation

Neuroinflammation is widely regarded as chronic, as opposed to acute, inflammation of the central nervous system.[5] Acute inflammation usually follows injury to the central nervous system immediately, and is characterized by inflammatory molecules, endothelial cell activation, platelet deposition, and tissue edema.[6] Chronic inflammation is the sustained activation of glial cells and recruitment of other immune cells into the brain. It is chronic inflammation that is typically associated with neurodegenerative diseases.

Causes of chronic neuroinflammation were following

- Toxic metabolites
- Autoimmunity
- Aging
- Microbes
- Viruses
- Traumatic brain injury
- Air pollution
- Passive smoke

➢**Foods that cause inflammation:** Most polyunsaturated vegetable oils like safflower, sunflower, corn, peanut and soy, are high in linoleic acid, an omega-6essential fatty acid that the body converts into arachidonic acid, another omega-6fatty acid that has a predominantly pro-inflammatory influence.

➢**Inflammation and menopause:** Changing levels of estrogen, progesterone, and testosterone have a role to play in age-related inflammation.

1.3 Factor Contributing To Inflamatory Disease

The word neuroinflammation has come to Stand for chronic, central nervous system (CNS) specific, inflammation-like glial responses that may produce neurodegenerative symptoms such as plaque formation, dystrophic neurite growth, and excessive tau phosphorylation.[8]

Neuroinflammation is distinct from inflammation in other organs, but does include some similar mechanisms such as the localized production of chemoattractantmolecules to the site of inflammation.[9]

1.3.1. Cytokines

Microglia activate the proinflammatory cytokines IL-1α, IL- 1β and TNF-α in the CNS. Cytokines play a potential role in neurodegeneration when microglia remain in a sustained activated state.[9]

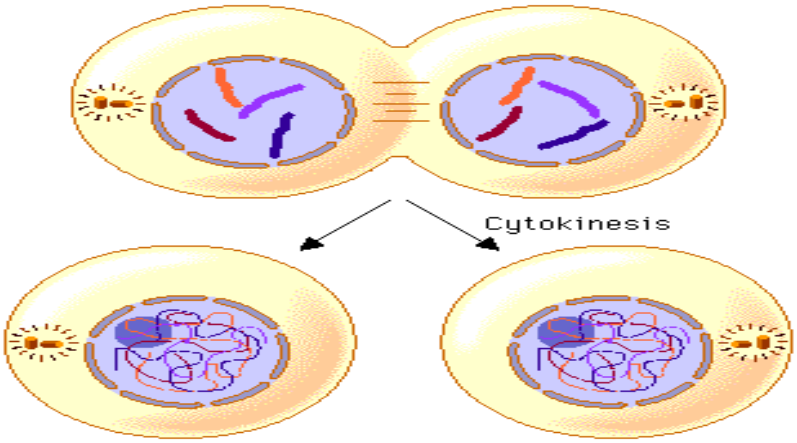

Fig No. 1 Cytokines

1.3.2Chemokines

Chemokines (Greek -kinos, movement) are a family of small cytokines, or signaling proteins secreted by cells. Chemokines are cytokines that stimulate directional migration of inflammatory cells in vitro and in vivo.[9] Chemokines are divided into four main subfamilies: C, CC, CXC, and CX3C. Microglial cells are sources of some chemokines and express the monocyte chemoattractant protein-1 (MCP-1) chemokine in particular.[9]

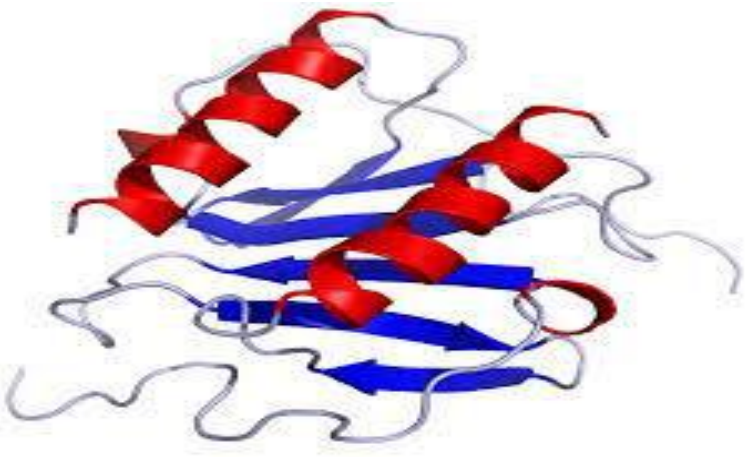

Fig No: 2 Chemokines

1.3.3. Proteases

When microglia are activated they induce the synthesis and secretion of proteolytic enzymes that are potentially involved in many functions.[9] There are a number of proteases that possess the potential to degrade both theextracellular matrix and neuronal cells that are in the neighborhood of the microglia releasing these compounds.[9]

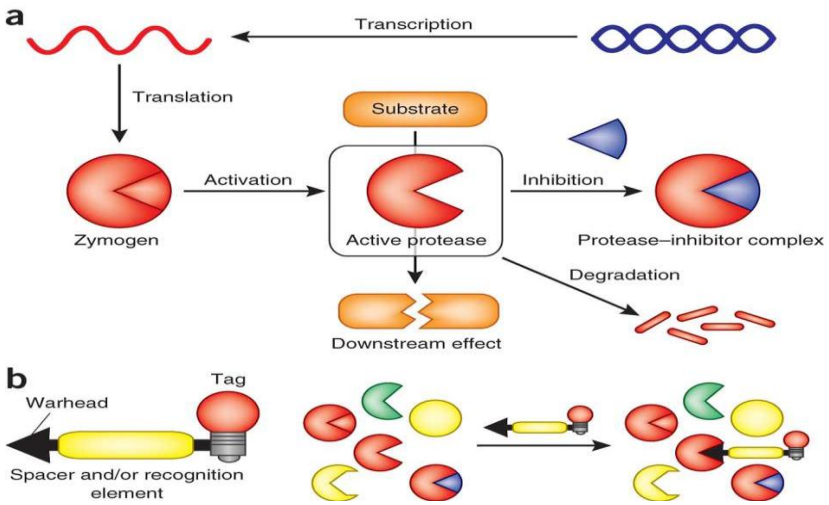

Fig N. 3 Proteases

1.3.4. Amyloid precursor protein

Microglia synthesize amyloid precursor protein (APP) in response to excitotoxic injury. Plaques result from abnormal proteolytic cleavage of membrane bound APP. Amyloid plaques can stimulate microglia to produce neurotoxic compounds such as cytokines, excitotoxin, nitric oxide and lipophylic amines, which all cause neural damage.

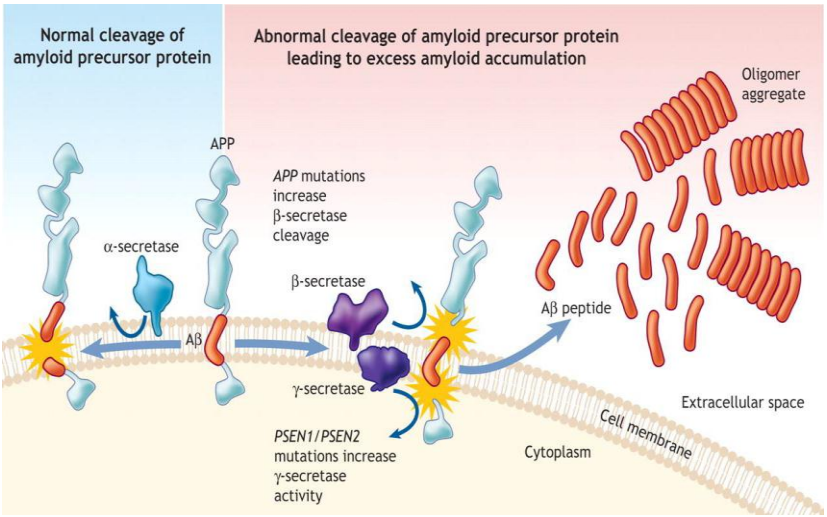

Fig No.4 Amyloid precursor protein

1.4 Importance of Neuroinflammation in Physiology and Disease State

1.4.1 Role of neuroinflammation in Physiology State

Neuroinflammation is a process in which the brain responds to infections, diseases and injuries through release of proinflammatory molecules.[10] In response to a brain insult, glial cells are the first to be activated. The astrocytes upon activation, increases expression of glial fibrillary acidic protein, and produces cytokines; also contributing to the formation of the glial scar, which isolates the damaged area. These reactive astrocytes produce neurotrophic factors such as nerve growth factor and brain-derivedgrowth factor which help in blood brain barrier repair and remyelination.[11]

a. Scavenging

This action is carried out in the ameboid and resting states. While moving through its set region, if the microglial cell finds any foreign material, damaged cells, apoptotic cells, neurofibrillary tangles, DNA fragments, or plaques it will activate and phagocytose the material or cell. In this manner microglial cells also act as "housekeepers" cleaning up random cellular debris.

b. Synaptic stripping

Post-inflammation microglia remove the branches from nerves near damaged tissue. This helps promote regrowth and remapping of damaged neural circuitry.

c. Promotion of repair

Post-inflammation, microglia undergo several steps to promote regrowth of neural tissue. These include synaptic stripping, secretion of anti-inflammatorycytokines, recruitment of

neurons and astrocytes to the damaged area, and formation of gitter cells. Without microglial cells regrowth and remapping would be considerably slower in the resident areas of the CNS and almost impossible in many of the vascular systems surrounding the brain and eyes.

d. Extracellular signaling

A large part of microglial cell's role in the brain is maintaining homeostasis in non- infected regions and promoting inflammation in infected or damaged tissue. Microglia accomplish this through an extremely complicated series of extracellular signaling molecules which allow them to communicate with other microglia, astrocytes, nerves, T- cells, and myeloid progenitor cells.

1.4.2 Role of neuroinflammation in Disease state

a. Alzheimer's disease: Alzheimer's disease (AD) is a progressive, neurodegenerative disease where the brain develops abnormalclumps (amyloid plaques) and tangled fiber bundles (neurofibrillary tangles). [12] There are many activated microglia over-expressing IL-1 in the brains of Alzheimer patients that are distributed with both Aβ plaques and neurofibrillary tangles. This over expression of IL-1 leads to excessive tau phosphorylation that is related to tangle development in Alzheimer's disease.[13] Many activated microglia are found to be associated with amyloid deposits in the brains of Alzheimer's patients. Microglia interact with β-amyloid plaques through cell surface receptors that are linked to tyrosine kinase based signaling cascades that induce inflammation.[14]

b. Human immunodeficiency virus: The infection of mononuclear phagocytes with HIV-1 is an important element in the development of HIV associated dementia complex (HAD). The only brain cell type that is "productively" infected with the virus are microglial cells. It has also become clear that neurotoxic mediators released from brain microglia play an important role in the pathogenesis of HIV-1.[15]

2 MECHANISM OF NEUROINFLAMMATION BY DIFFERENT MEDIATOR

2.1 Cellular and molecular mechanism of neuroinflammation

It consist of three process

2.1.1 Exudation of Leukocytes

2.1.2 Phagocytosis

2.1.3 Vascular change

2.1.1 Exudation of Leukocytes

The escape of Leukocytes from the lumen of flow of microvascular to the interstitial tissue is the most important feature of inflammatory response.

a. Change in the formed element of blood

The rate of flow of blood is increased due to vasodilation. There is a slowing or stasis of blood stream with stasis change in the normal axial flow of blood in the microcirculation take place.

b. Rolling and Adhesion

Neutrophils slowly roll over the endothelial cells lining the vessels wall is a Rolling phase and this is followed by the transient blood between the leucocytes and endothelial cells becoming firmer is a Adhesion Phase.

c. Emigration

The Neutrophils lodged between the endothelial cells and basement membrane cross the basement membrane by damaging it locally with secreted collagenases and escape out into the extravascular space this is aknown as Emigration.

d. Chemotaxis

The chemotactic factor mediated transmigration of leucocytes after crossing several barriers (endothelium basement membrane, perivascular, myofibroblast and matrix) to reach the interstitial tissue is called chemotaxis

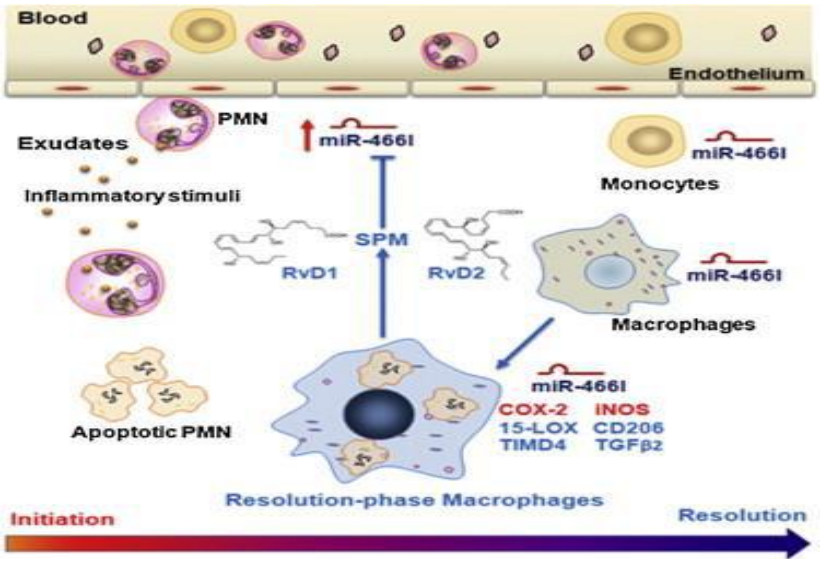

Fig No. 5 Exudation of Leukocytes

2.1.2 Phagocytosis

The process of engulfment of solid particulate material by the cell. The cells performing this function are called phagocytes.

There are two type of phagocytic cells

I. Polymorphonuclear neutrophils (PMNS) which appear early in acute inflammatory response also called as microphages.

II. Circulating monocytes and fixed tissue mononuclear phagocytes called as Macrophages. The process of phagocytosis involve the following four steps were following

a. Recognition and attachment stage(opsonisation)
b. Engulfment stage.
c. Secretion (degranulation) stage.
d. Digestion or degradation stage.

2.1.3 Vascular change

Alteration in vessel caliber resulting in increased blood flow (vasodilation) and structural changes that permit plasma protein to leave the calibration (increased vascular permability).

It include were following

a. Change in vascular caliber and flow
b. Increased vascular permeability

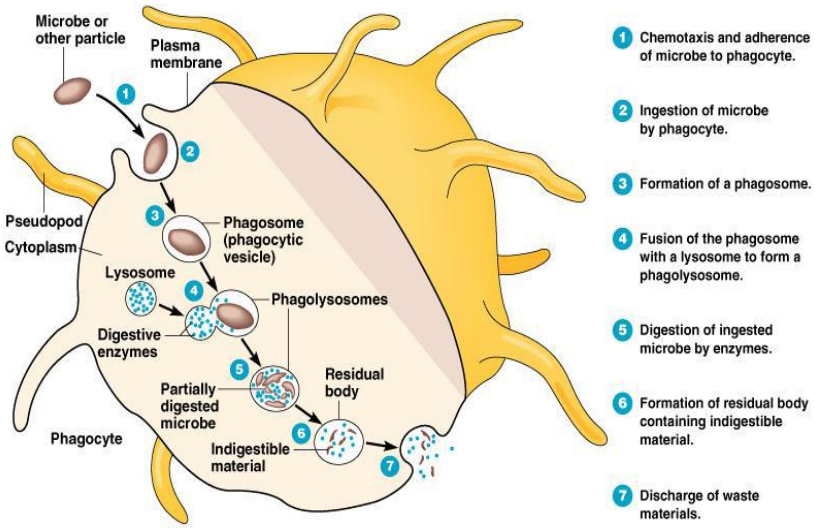

Fig No. 6 Phagocytosis

2.2 Explanation of Mechanism of mediator in detail

Microglia and astrocytes secrete multi-functional immunoregulatory proteins called cytokines, most notably Tumor Necrosis Factor-α (TNF), the interleukin-1 (IL-1) andinterleukin-6 (IL-6) families, interferon gamma (IFNγ), and Transforming Growth Factor beta (TGF-β), all of which act in context-dependent ways to modulate inflammatory processes and the permeability of the BBB (11, 44, 45). Cytokines can exert neuroprotective effects independent of their immunoregulatory properties and synaptic plasticity (46). In other conditions, cytokines as well as chemoattractant factors called chemokines promote apoptosis of neurons, oligodendrocytes, and astrocytes and cause damage to myelinated axons.

They are also called as permeability factors or endogenous mediator of increased vascular permeability, these are large and endogenous compound which can enhance vascular permeability. The substance acting as chemical mediator of inflammation may be released from the cell the plasma or damaged tissue itself.

They are broadly classified into 2 groups were following

2.2.1 Mediator released by cell.

2.2.2 Mediator originating from cell.

2.2.1 Mediator released by cell.

a. Histamine

- It is stored in the granules of mast cell, basophils and platelets.
- Stimuli or substance inducing acute inflammation i.e heat, cold, irradiation, trauma, irritant chemical.
- histamine releasing factors from neutrophils, monocytes, platelets.
- Interleukins.

b. Prostaglandins

P4D2 and P4E2 act on blood vessels to causes increased venular permeability ,vasodilation and inhibit inflammatory cell function.

c. Thromboxane

Vasoconstrictor and bronchoconstristor and enhances inflammatory cell function by causing platelet aggregation.

d. Leukotrines

While LTC4, LTD4 and LTE4 have common action by causing smooth muscles contraction and thereby induce vasoconstriction , bromoconstriction and increased vascular permeability .

e. Granules of neutrophils

The inflammatory cell neutrophils contain lysosomes granules which on release elaborate a variety of mediators of inflammation.

f. Granules of monocytes and tissue macrophages

These cells on degranulation also release mediators of inflammation like acid proteases, collagenase, elastase.

g. Platelet activating factor (PAF)

It is released from IgE sensitized barophils or mast cells other leucocytes,endothelium and platelet . The action of PAF as mediator of inflammation are

- Increased vascular permeability.
- Vasodilatation in low concentration and vasoconstriction otherwise.
- Bronchoconstriction
- Adhesion of leucocytes to endothelium.
- Chemotaxis

h. Cytokines

They are polypeptide substance produced by activated lymphocytes (lymphokines) and activated monocytes (monokines) main cytokines acting as mediator of inflammation are :- interleukin-1 (IL-1), tumour nechrosis, interferon (IF)-7 and chemokines (IL-8, PF-4).

i. Nitric oxide and Oxygen metabolite

Nitric oxide was vascular relaxation factor produced by endothelial cell. Nitric oxide plays the following role in inflammation i.e

- Vasodilatation
- Anti-platelet activating agent.
- Possible microbicidal action.

2.2.2 Mediator originating from cell.

These include the various products derived from activation and interaction of 4- interlinked system i.e

a. Kinin system: This system activation by factor XII a generates bradykinin. Bradykinin act in the early satge of inflammation and its effect include

- Smooth muscles contraction,
- Vasodilation,
- Increased vascular permeability,
- Pain.

Factor XII

↓

Contact

↓

Factor XII a

↓

Prekallikrein activator

↓

Plasma Prekallikrein

↓

Kallikrein

↓

Kininogen

↓

BRADYKININ

Fig No. 7

b. The clotting system

Factor XIIa initiates the cascade of the clotting system resulting information of fibrinogen which is acted upon tin thrombin to form fibrin and fibrinopeptide . The action of fibrino peptide in inflammation are

- Increased vascular permeability
- Chemotaxis for leucocyte.
- Anticoagulant activity

c. Plasminogen activator

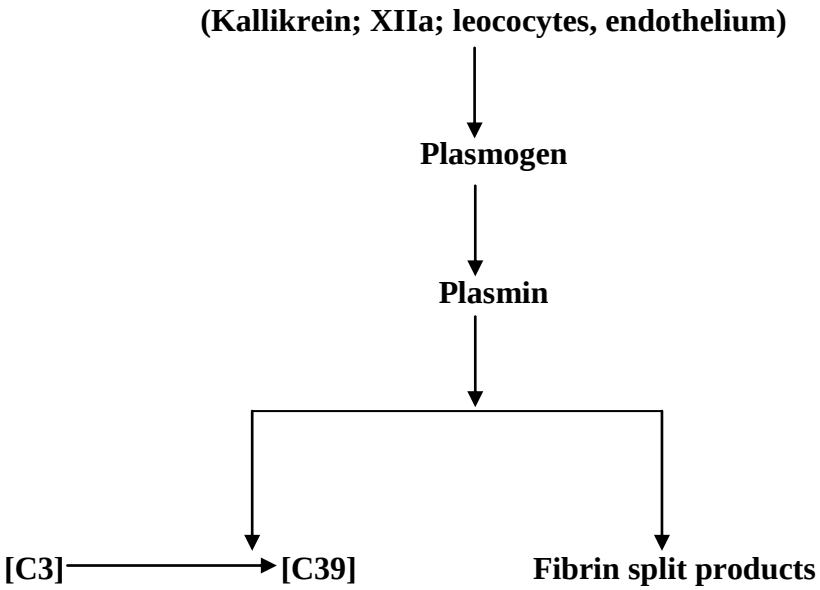

Fig No. 8

d. The component system

-The classic pathway through antigen – antibody complexes.

-The alternate pathway via non-immunologic agent such as bacterial toxins, Cobra venoms and IgA.

2.3 Mechanism for physiological balance

a. Recurrent attack of acute inflammation

When repeated bouts of acute inflammation culminate in chronicity of the process e.g in recurrent urinary tract infection leading to chronic pyelonephritis

b. Neuroinflammation starting denova

Whem the infection with the organism of low pathogenerty is chronic from the begning. E.g.infection with mycobacterium tuberculosis

c. Mononuclear cell filteration

Mononuclear inflammatory cells like phagocytes and lymphoid cells. Pahgocytes are represented by circulating monocytes, tissue,macrophages,epithrlioid cells and sometime multinucleated gaint cells.

d. Tissue destruction or Necrosis

Tissue destruction or Necrosis are central feature of most form of chronic inflammatory . This is brought about by activated microphages which release a variety of biologically active

substance e.g. protease, elastase, collagenase, lipase, reactive oxygen radicals, cytokines, nitric oxide angiogenesis growth factor.

e. Proliferative changes

Proliferation of small blood vessels and fibroblast is stimulated resulting information of inflammatory granulation tissue eventually, healing of fibrosis and collagen laying takr places.

f. Chronic granulomatous inflammation

Its characterized by formation of granulomas. E.g. tuberculosis, leprosy, syphilis, actinomycosissss, sarcoidosis.

2.4 Mechanism of disease state

2.4.1 In viral infections i.e Human immunodeficiency virus

The infection of mononuclear phagocytes with HIV-1 is an important element in the development of HIVassociated dementia complex (HAD). The only brain cell type that is "productively" infected with the virus are microglial cells. It has also become clear that neurotoxic mediators released from brain microglia play an important role in the pathogenesis of HIV-1. "HIV-1 can enter the microglial cell via CD4 receptors and chemokine co-receptors such as CCR3, CCR5, and CXCR4, with CCR5 being the most important of these. Interestingly, humans with double allelic loss of CCR5 are virtually immune to HIV acquired via the sexual route though can be infected by IV transmission of CXCR4 tropic viruses. IL-4 and IL-10 enhance the entry and replication of HIV-1 in microglia through the up-regulation of CD4 and CCR5 expression, respectively. The chemokines CCL5/RANTES, CCL3/MIP-1α, CCL4/MIP-1β, all of which bind to CCR5, are inhibitory to HIV-1 replication in microglial cells, apparently by their ability to block viral entry." Infected microglia contain viral particles intracellularly. There is a correlation between the severity of dementia and microglial production of neurotoxins.[15]

2.4.2 In bacterial infections i.e Streptococcus pneumonia

Lipopolysaccharide (LPS) is the major component of the outer membrane of a gram- negative bacterial cell wall. LPS has been shown to activate microglia in vitro and stimulates microglia to produce cytokines, chemokines, and prostaglandins.[15] "Although LPS has been used as a classic activating agent, a recent study of rat microglia demonstrated that prolonged LPS exposure induces a distinctly different activated state from that in microglia acutely

exposed to LPS." *Streptococcus pneumoniae* is the most common cause of bacterial meningitis. It is primarily localized to the subarachnoid space while cytokines and chemokines are produced inside the blood brain barrier. Microglia interact with streptococcus via their TLR2 receptor; this interaction then activates microglia to produce nitric oxide which is neurotoxic. [16] The inflammatory response, triggered by microglia, may cause intracerebral edema**.**

2.4.3 In parasitic infections

Plasmodium falciparum is a parasite that causes malaria in humans.[15] A serious complication of malaria is cerebral malaria (CM).[15] CM occurs when red blood cells break through the blood brain barrier causing microhemorrhages, ischemia and glial cell growth. This can lead to microglial aggregates called Durck's granulomas. Recent research has indicated that microglia play a major role in the pathogenesis of CM.[15]

2.4.4 Role in neuropathic pain

Microglia have been implicated in neuropathic pain. They become activated in response to nerve injury, as demonstrated by several animal models.[17] Activated microglia release substances that excite painsensitive neurons, including prostaglandins and reactive oxygen species, through the purinergic signaling mechanisms.[18, 19] Moreover, microglia also release of proinflammatory molecules through the stimulation of purinergic receptors, including IL1-β, IL-6,and TNF-α.[20, 21, 22] The release of these molecules is mediated by the P2X7 receptor and creates a positive feedback loop, exacerbating the pain response.[23]

3. FUTURE PROPESTUS

Target for different disease were following

3.1 Inhibition of activation

One way to control neuroinflammation is to inhibit microglial activation. Microglia have shown that they are activated by diverse stimuli but they are dependent on activation ofmitogen-activated protein kinase (MAPK). Recently, minocycline (a tetracycline derivative) has shown down-regulation of microglial MAPK. Another promising treatment is CPI-1189, which induces cell death in a TNF α-inhibiting compound that also down-regulates MAPK.[24] Recent study shows that nicergoline (Sermion) suppresses the production of proinflammatory cytokines and superoxide anion by activated microglia.[25] Microglial activation can be inhibited by MIF (microglia/macrophage inhibitory factor, tuftsin fragment 1– 3,Thr-Lys-Pro).

3.2 Inhibition of amyloid deposition

Inhibitors of amyloid deposition include the enzymes responsible for the production of extracellular amyloid such as β-secretase and γ-secretase inhibitors. Currently the γ- secretase inhibitors are in phase II clinical trials as a treatment for Alzheimer's disease but they have immunosuppressive properties, which could limit their use. Another strategy involves increasing the antibodies against a fragment of amyloid. This treatment is also in phase II clinical trials for the treatment of Alzheimer's disease.[26]

3.3 Inhibition of cytokine synthesis

Glucocorticosteroids (GCS) are anti-inflammatory steroids that inhibit both central and peripheral cytokine synthesis and action. Both lovastatin and sodium phenylacetate were found to inhibit TNF-α, IL-1β, and IL-6 in rat microglia.[27] This shows that the mevalonate pathway plays a role in controlling the expression of cytokines in microglia and may be important in developing drugs to treat neurodegenerative diseases. Naltrexone may provide a solution to the inflammatory mediators produced by microglia. Although naltrexone's main action is to competitively bind to opioid receptors, new research shows that naltrexone, when given in low doses once per day (low-dose naltrexone), can inhibit cytokine synthesis by microglia cells. This mechanism is still being investigated, but there are already studies that indicate that it helps some patients suffering from fibromyalgia syndrome. Naltrexone shows more promise than GCSs because the GCSs inhibit immune system function more generally, increase allergic reactions and, as the name implies, increase blood glucose levels.[28, 29]

4. CONCLUSION

It is clear that glial cells participate in the process of neurotoxicity development in both chemical and environmental insults, with physical injury, and in neurodegenerative disease. Cells of the CNS such as neurons, astrocytes, and microglia along with pattern recognition receptors, cytokines, chemokines, complement, peripheral immune cells, and signal pathways form the basis for neuroinflammation. .In pro-inflammatory cytokines or a structural morphological alteration in microglia is relatively easy; determining the overall effect of these changes and their underlying biological justification is a much more complicated effort.

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