IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

ROLE OF NEUROGLIAL CELLS IN NEUROINFLAMMATION

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ABSTRACT

Glial cells throughout the nervous system are closely associated with synapses. Accompanying these anatomical couplings are intriguing functional interactions, including the capacity of certain glial cells are to respond and modulate neurotransmission. Glial cells can also help establish, maintain, and reconstitute synapses. Neuropathic pain refers to a variety of chronic pain conditions with differing underlying pathophysiologic mechanisms and origins. A common underlying mechanism of neuropathic pain is the presence of inflammation at the site of the damaged or affected nerve(s). This inflammatory response initiates a cascade of events resulting in the concentration and activation of innate immune cells at the site of tissue injury. The release of immunoreactive substances such as cytokines, neurotrophic factors, and chemokines initiate local actions and can result in a more generalized immune response. The resultant neuroinflammatory environment can cause activation of glial cells located in the spinal cord and the brain, which appear to play a prominent role in nociception. Glial cells, also known as neuroglia, are nonconducting cells that modulate neurotransmission at the synaptic level. Glial cells can be subdivided into two primary categories: microglia and macroglia, which include astrocytes and oligodendrocytes. Astrocytes and microglia are known to play a role in the development, spread, and potentiation of

neuropathic pain. Microglia propagate the neuroinflammation by recruiting other microglia and eventually activating nearby astrocytes, which prolongs the inflammatory state and leads to a chronic neuropathic pain condition. Our review focuses on the role of glia and the immune system in the development and maintenance of neuropathic pain.

Keywords: Microglia; Astrocyte; Glial activation; Neuroinflammation; CNS; Interaction

INTRODUCTION

Glial cells were long believed to be simple support cells for neurons. Given this perception, the revelation that some of these cells engage in dynamic interactions with synapses during neurotransmission-the most quintessential neuronal function-was surprising. Evidence shows that glial cells can respond to neurotransmission, modulate neurotransmission and instruct the development, maintenance, and recovery of synapses. In fact, many synapses have a glial contribution that modulates information flow between neurons. Based on the criteria, we will discuss how glial cells can affect neurotransmission at synapses wherever possible, in situ examples will be highlighted.

A neuron is also known as a nerve cell is electrically excitable and processes and transmits information through electrical and chemical signals.

NEUROGLIA

- A group of different cells, collectively called neuroglia or glial cells are found in the nervous system. Their purpose is to improve the functionality of neuron activity and support them in a various ways.
- The nervous system is broken down into two divisions. The central nervous system (CNS) and the peripheral nervous system (PNS). Each of these systems contains its own neuroglia.
- Neuroglia ---- Neuro (Neurons) - Glia (Glue).
- It is supporting cells of the nervous system.
- These are non-excitable do not transmit nerve impulse number of glial cells is to times greater than neurons 10:1 and less than 1:1.

Main functions of glial cells

- To surround neurons and hold them in place.
- To supply nutrients and oxygen to neurons.
- To insulate one neuron from another neuron.
- To destroy pathogens and remove dead neurons.
- Repair of neurons after injury.

- Maintain homeostasis.

Different types of neuroglial cells

There are two types of neuroglial cells they are

A. Central neuroglial cells(CNS)

B. Peripheral neuroglial

cells(PNS) The Central Neuroglial

cells are

- Astrocytes
- Oligodendrocytes
- Microglia
- Ependymal cells

The peripheral neuroglial cells are

- Schwann cells
- Satellite cells

ASTROCYTES

- These are the star-shaped consist of fibrous (White matter) & processes cover synapse from the blood-brainbarrier.
- It is most abundant at their free end has small swelling(foot processes).
- Found in large numbers adjacent to blood vessels with their foot processes like a sleeve round them.
- Blood is separated from the neurons by capillary walls and astrocytes foot processes called blood-brainbarrier.
- Astrocytes are cells that contain extensions which wrap around neurons.
- They not only provide physical support to neurons and hold them in place but also connect the neurons tothe blood supply.
- They help to maintain the ion and nutrient concentration outside the neurons.

Functions

- Supporting network in brain.
- Maintain chemical environment of ECF.
- Recycle neurotransmitters.
- Physical and metabolic support for neurons , detoxification guidance during migration, regulation of energy metabolism, electrical insulation, transport of blood-borne material to the neuron and reaction to injury.

OLIGODENDROCYTES

- Oligodendrocytes and Schwann cells are the myelin-forming cells of the nervous system.
- Schwann cells are present in the periphery, and oligodendrocytes are in the central nervous system.
- Myelin is composed of layered phospholipid membranes and serves to support and insulate axons,allowing for faster impulse transduction.
- Saltatory conduction occurs as the impulses jump across sodium ion-rich nodes of Ranvier.
- One oligodendrocyte myelinates multiple axons.
- Oligodendrocytes are incapable of replication upon injury.

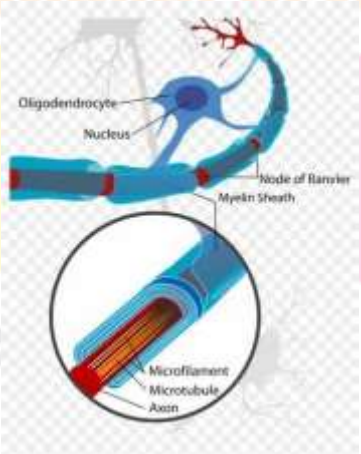


Fig:Oligodendrocyte

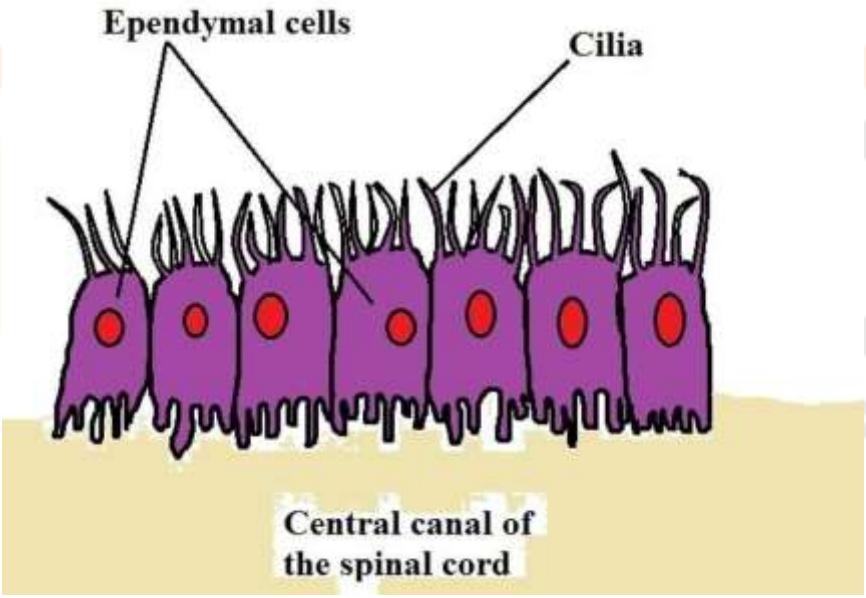
Functions

- Oligodendrocytes are primarily responsible for maintain and generation of the myelin sheath and that surrounds axons.
- They also participate in axonal regulation and the sculpting of higher order neuronal circuits.

EPENDYMAL CELLS

- Ependymal cells which create cerebral spinal fluid (CSF) line the ventricles of the brain and central canal of the spinal cord.
- These cells are cuboidal to columnar and have cilia and microvilli on their surfaces to circulate and absorb cerebral spinal fluid.
- Ependymal cells are smaller than astrocytes. Ependymal cells encompass three types of cells:

1. EPENDYMOCYTES: Line the ventricles of the brain and central canal of the spinal cord. There are relatively abundant and are involved in the connection between the CSF and nervous tissue.
2. TANYCYTES: Line the floor of the third ventricle overlying the median eminence of the hypothalamus.
3. CHORODIAL EPITHELIAL CELLS: Line the surface of the choroid plexus and are involved in theregulation of CSF.



Functions

- The ependymal cells have many important functions in the developing brain that they are no longer needed in the mature brain.
- In the adult brain they are responsible for the transport of electrolytes and some solutes between t h e cerebrospinal fluid and the brain parenchyma.

MICROGLIA

Microglia are the mesoderm-derived resident macrophages of the CNS. As such, they phagocytose and remove foreign or damaged material cells or organisms. They are small, relatively sparse cells.

- Microglia act as the brain's resident clean-up squad by phagocytizing apoptotic cells, plaques, andpathogens.
- Because they can prune and reshape synapses, microglia may also be influential in the pathogenesis ofpsychiatric illness.
- Microglia have specific receptors on their surface which recognize distress signals from other cells.
- These signals attract microglia tothe site of the problem.
- When the brains balance is disturbed living neurons can become stressed and produce these signals.
- This may cause them to be eaten alive by microglia. As the neurons are also killed the connections they have with their neurons are also eliminated, which can cause severe issue in brain connectivity and functions.
- Microglia exhibit several features that distinguish them from other populations of macrophages, such as their "ramified" branches that emerge from the cell body and communicate with surrounding neurons and other glial cells.
- Microglia can rapidly respond to infectious and traumatic stimuli and adopt a "phagocytotic" nature. Activated microglia are known to produce many proinflammatory mediators including cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide which mainly contribute to the clearance of pathogens or infections.
- However, prolonged or unwarranted microglial cell activation may result in pathological forms of inflammation which can lead to several neuroinflammatory conditions of the nervous system.

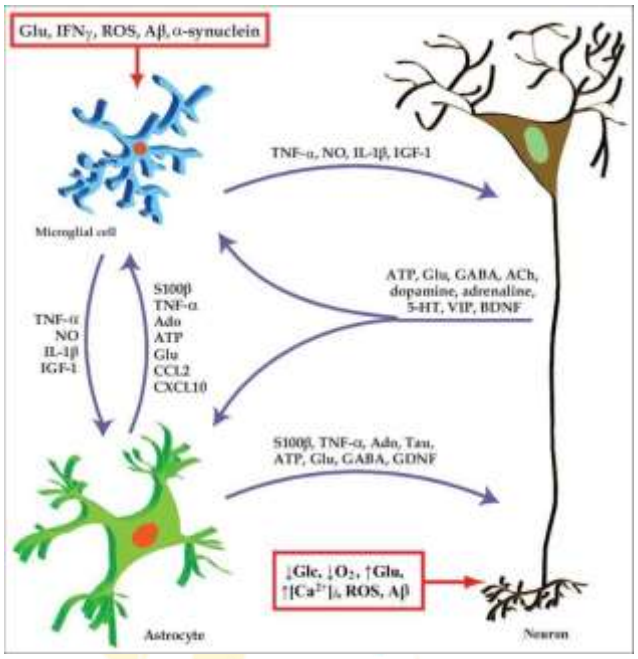


Fig: Signaling Systems in Microglia in Neurons

Functions

- Microglia are the primary immune cells of the central nervous system, similar to peripheral macrophages.
- They respond to pathogens & injury by changing morphology and migrating to the site ofinfection/injury,where they destroy pathogens and remove damaged cells.

SCHWANN CELLS

Glial cells that myelinate the axons of peripheral nerves. These cells wrap their cytoplasm in a spiral fashion around short segments of axons. Because the myelin sheath is formed from numerous Schwann cells arranged sequentially along the axon, there are gaps between adjacent myelinating cells producing mmyelinfreefree areasthe axon called nodes of Ranvier. These play an important role in nerve impulses. Organization of myelinating Schwann cells. Schematic organization of myelinating Schwann cells (blue) surrounding an axon (gray); the left cell is shown in longitudinal cross-section and the right cell is shown unwrapped. Myelinating Schwann cells are surrounded by a basal lamina (illustrated only on the left). The abaxonal compartment contains the Schwann cell nucleus (SN); it is divided into Cajal bands and periodic appositions that form between the abaxonal membrane and the outer turn of compact myelin. The Schwann cell and axonal membrane is separated from the axonal membrane by the periaxonal space (shown in yellow).

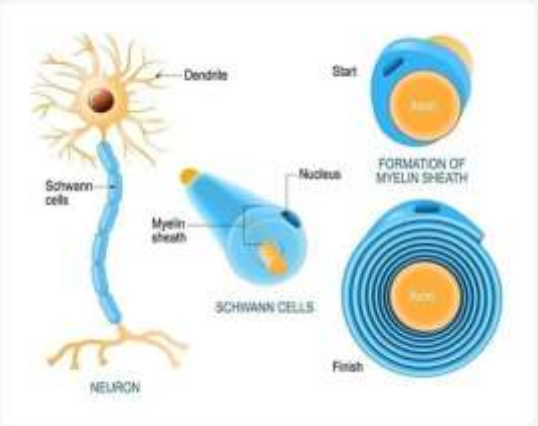


Fig: Schwann cells

DISEASES OF NEUROGLIAL CELLS

Dysfunction in glial cells is associated with a variety of brain diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, glioblastoma, autism, and psychiatric disorders.

ALZHEIMER'S DISEASE

Alzheimer's disease is a neurodegenerative disease that is the most common cause of dementia.Dementia is a set of symptoms of poor memory and difficulty learning. Two major factors in the progression of Alzheimer's disease are

1. Beta-Amyloid Plaques
2. Neurofibrilllary Tangles

1. **BETA-AMYLOID PLAQUES**:

Amyloid plaque, consisting of extracellular deposits beta-amyloid protein in selective areas of the brain such as cortex, hippocampus, amygdala, subcortical nuclei, etc.

- Pamilial AD results from mutations in the genes for amyloid precursor protein (APP) which causes an increase in beta-amyloid protein formation.

2. **NEUROFIBRILLARY TANGLES**:

Intraneuronal neurofibrillary tangles comprise the aggregates of highly phosphorylated form of normal neuronal protein.

- The relationship of these neurofibrillary tangles to neurodegeneration is not known.
- It is still not clear whether the neuritic plaques and or the tangles are causative factors or the by-productof free radical damage leading to brain degeneration.

PARKINSON'S DISEASE

It is a chronic progressive disease of the nervous system characterized by the cardinal features of rigidity,bradykinesia, tremor, and postural instability.

Fig: Symptoms of Parkinson Disease

TREMOR:

It is an involuntary oscillation of body parts occurring at a slow frequency of 4to 6 HZ. Two types of tremors are:

1. Resting tremor
2. Postural tremor

1. RESTING TREMOR:

It is typically present at rest and disappears with voluntary movement. Resting tremors may also be seen in the forearm, jaw, or tongue.

2. POSTURAL TREMOR:

It is seen in the head and trunk when the patient tries to maintain an upright position against gravity and completely diminishes during sleep.

GLIOBLASTOMA

It is the most common malignant primary tumor of the brain and it is very aggressive, involving glial cells. Glioblastoma differs in a location within the central nervous system, in age and sex distribution, in growth, in invasiveness, in historical features, in progression, and in response to therapy. The exact cause is unknown butchanges or loss of chromosome 17 and inactivation of P53 have a role

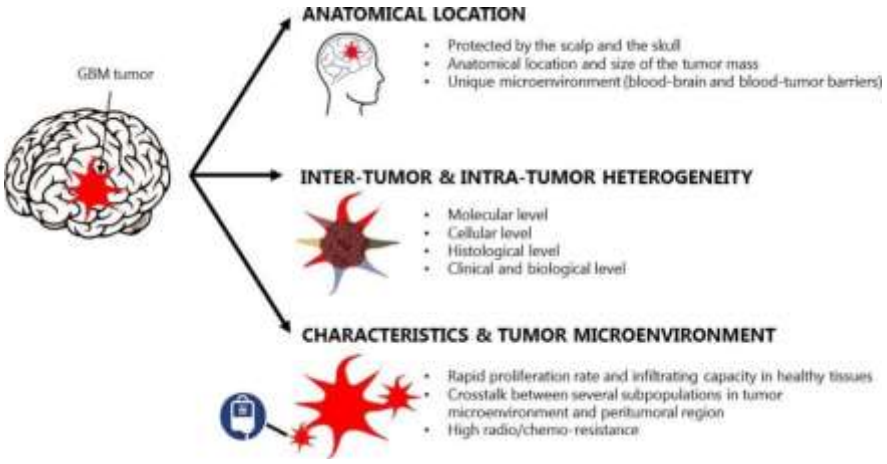


Fig: Characteristics and Location of Glioblastoma

MULTIPLE SCLEROSIS

Multiple sclerosis is a chronic demyelinating disease that affects the myelin sheath of neurons in the central nervous system. The course of the illness varies from person to person and the four clinical patterns have been identified

1. Relapsing-Remitting Multiple Sclerosis:

   Episodes of acute worsening with recovery and a stable course between relapses.

2. Primary Progressive Multiple Sclerosis:

   Gradual, nearly continuous neurologic deterioration from the onset of manifestations.

3. Secondary Progressive Multiple Sclerosis:

   Gradual neurologic deterioration neurologic deterioration with or without superimposed Acute relapses in a client who previously had relapsing-remitting multiple sclerosis.

4. Progressive Relapsing Multiple Sclerosis:

   Gradual Neurologic deterioration from the onset of manifestations but with subsequent superimposed relapses

NEUROTONICS

It is strengthening or stimulating impaired nervous action. An agent that improves the tone of a force of the nervous system.

HERBAL DRUGS USED IN NEUROTONICS

There are different types of herbal medicines or drugs used in neuro tonics. They are:

1. Chamomile
2. Valerian

1. CHAMOMILE

Chamomile is one of the most medicinal herbs to mankind. It is the Member of Asteraceael Compositae family. Chamomile contains many terpenoids and flavonoids contributingto its medicinal properties.

Fig: Chamomile

SCIENTIFIC EVALUATION OF CHAMOMILE

A. Anti-inflammatory and Antiphlogistic properties

- The flowers of chamomile contain 1-2% of volatile oil including alpha-bisabolol,alpha-bisabolol oxides A and B,and matricin usually converted to chamazulene and other flavonoids which posses anti-inflammatory and antiphlogistic properties.
- Essential oil penetrate below the skin surface into the deeper skin layers.
- One of thr chamomile's anti-inflammatory activities involves the inhibition of LPS-induced prostaglandin E release and attenuation of cyclooxygenase (COX-2) enzyme activity without affecting the constitutive form, COX-1.

B.D iabetes

Chamomile ameliorates hyperglycemia and diabetic complications by suppressing blood sugar levels, increasing liver glycogen storage, and inhibiting sorbitol in the human erythrocytes. The pharmacological activity of chamomile extract has been shown to be independent of insulin secretion and studies further reveal its positive effect on pancreatic beta cells in diminishing hyperglycemia-related oxidative stress.

2. Valerian

- Valerian has been used medicinally since the times of early Greece and Rome.
- Historically, valerian was used to treat insomnia, migraine, fatigue, and stomach cramps.
- Valerian is promoted for insomnia, anxiety, depression, menopause symptoms, and headache.
- The roots and rhizomes (underground stems) of valerian are used for medicinal purposes.

Fig: Valerin

Constituents

- The biochemical active components of valerian extract are alkaloids: actinidine, creatinine, isovalerate,valerian.
- Free amino acids such as Gamma-aminobutyric acid (GABA), tyrosine, arginine, and glutamine.
- Iridoids(valepotriates), esters non-glycosidic, firstly acevaltrate, isovaltrate and valtrate.
- Volatile oil containing active sesquiterpenes(acetoxivalerenic acid, valerenic acid).
- Flavanones such as hesperidin, 6-methylapigenin, and Furano Furano linarin.
- The main component of valerian is a yellowish-green to brownish-yellow oil, which is present in the driedroot varying from 0.5 to 2% through an average yield that rarely exceeds 0.8%.
- The oil is contained in the sub-epidermal layer of cells in the root, not in isolated cells or glands. It is of complex composition, containing valerianic, formic, and acetic acids, the alcohol known as borneol and pinene.
- The valerianic acid present in the oil is not the normal acid, but isovaleric acid, an oily liquid that isthe source of the characteristically unpleasant odor or valerian.

Medicinal uses

- The root of valerian is used most commonly for its sedative and hypnotic properties in patients with insomnia.
- Valerian also influences the circulation, by slowing the heart and increasing its force, it has been used in the treatment of cardiac palpitations and irregular beats. It is also believed to be useful in lowering blood pressure.
- Valerian is often indicated during the tapering of benzodiazepines such as clonazepam and diazepam.

SYNTHETIC DRUGS USED IN NEUROTONICS

Synthetic drugs or new psychoactive substances(NPS), aim to mimic the effects of existing illicit drugs suchas cannabis, cocaine, MDMA, LSD.

Types of Synthetic Drugs

1. Synthetic cannabinoids
2. Phenethylamines
3. Synthetic cathiones
4. Piperazines
5. Novel benzodiazepines

1. Synthetic cannabinoids

- Synthetic cannabinoids are a class of molecules that bind to the same receptors to which the cannabinoidsin cannabis plants attach. They are designer drugs, commonly sprayed on to plant matter and usually smoked, although they have also been ingested as a concentrated liquid form in the US and UK since 2016.

Fig:CANNABINOIDS

Effects of Synthetic Cannabinoids

A. Synthetic cannabinoids produce a similar effect to smoking cannabis. Reported effects include: Euphoria
B. Spontaneous laughter and excitement
C. Increased appetite
D. Dry mouth
E. Quite and reflective mood

2. Phenethylamines

- Phenethylamines are a group of psychoactive drugs which include amphetamines and MDMA.
- This group also includes synthetic hallucinogens such as the synthetic NBOMes, benzofurans(bromodragonfly) EX: NBOMes can be in the form of blotting paper like LSD. They can also be found in pill or powder form.

3. Synthetic Cathinones

- Synthetic cathinones are a group of drugs relating to the khat plant. These drugs are stimulants and mimicthe effects of amphetamines by speeding up the messages between the brain and body.

- Synthetic cathinones mostly take the form of brown powder, but can also appear as small, chunky crystals.Sometimes they are found in capsule or tablet form.

4. Piperzines

- Piperazines are a group of chemicals that mimic the effects of MDMA. These synthetic drugs are often sold as MDMA and are available as a pill, capsule or powder.
- Some common piperazines are 1-benzylpiperazine(BZP) and trifluoromethyl phenylpiperazine(TFMPP).when these two chemicals are combined,they can have similar effects to MDMA

5. Novel Benzodiazeepines

- Novel benzodiazepines may be sold under the names 'Legal Benzodiazepines', or 'research chemicals'.
- These include chemicals that were tested but not approved for medicinal purposes, or manufacturedsubstances with a different structure from existing benzodiazepines.
- There is a limited understanding of the short- and long- term health impacts of benzodiazepines.
- Symptoms of with drawl from novel benzodiazepines can include:
    A. Headache
    B. Dizziness and tremors
    C. Nausea, vomiting, stomach pains
    D. Seizures.

Conclusion

The glial cells are probably the most versatile cells in our body based on their characteristics and function: migration, neural protection, proliferation, axonal guidance, and trophic effect. Glial cells are supporting cellsof the nerve tissue that nourish, protect and support the neurons and form an insulating, myelin sheath aroundthem. Most of these cells are compared to connective tissue cells thanks to their function and are called nervetissue supporting cells.

In addition to the undoubted supporting role, glial cells have many other functions, including the role in building the myelin sheath around the axon in the CNS Oligodendrocytes and in the PNSSchwann cells, participating on the healing process after brain injury, maintaining ion homeostasis(especially K+ions) and PH of extracellular fluid, synthesizing the precursors of some neurotransmitters, such as glutamine(glutamate chemical mediator precursor), and the role of being brain macrophages because they turninto phagocytes during any inflammation or injury.

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