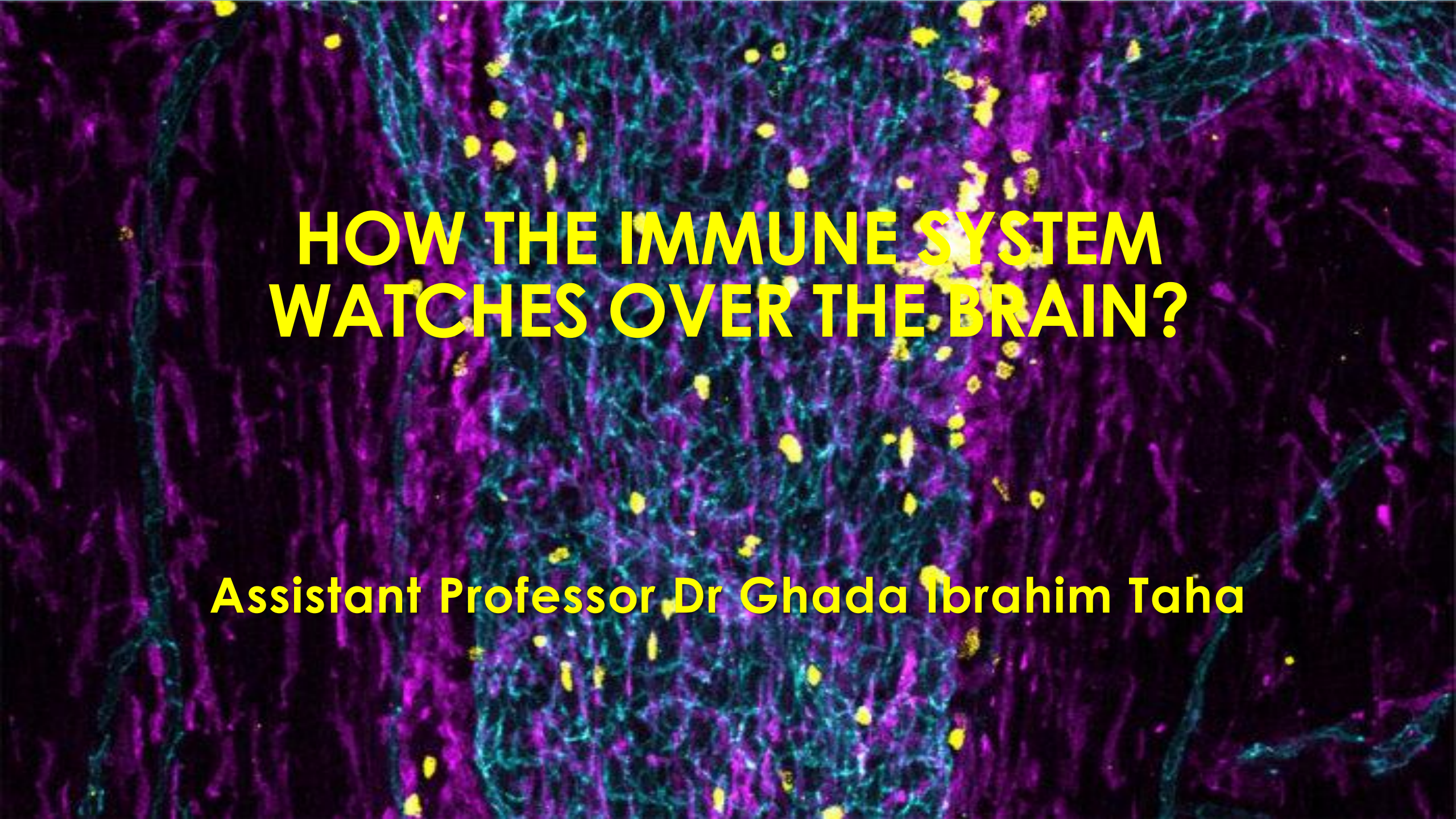


HOW THE IMMUNE SYSTEM WATCHES OVER THE BRAIN?

Assistant Professor Dr Ghada Ibrahim Taha

- Generations of students have learned that the central nervous system has "immune privilege." This means that — to an extent — the immune system tolerates the presence of foreign proteins, or antigens, and tissue in the brain and spinal cord.
- The immune system cannot respond in the usual way to infections, injuries, or tumors in the brain and spinal cord, because the blood-brain barrier prevents immune cells from entering or leaving.
- **A study has now identified border "checkpoints" where the immune system monitors fluid leaving the brain for signs of infection.**
- **The discovery offers new possibilities for treating brain diseases, such as multiple sclerosis (MS).**

- **Scientists know that inflammation plays a pivotal role in many neurological and psychiatric conditions, including Alzheimer's disease, MS, autism, and schizophrenia.**
- So the question remains, how does the immune system respond to and influence the brain in such a broad range of conditions?
- A team of scientists led by Washington University School of Medicine in St. Louis, MO, have discovered that immune cells are stationed in the dura mater, which is the tough outer membrane of the brain.
- From this vantage point, they monitor the cerebrospinal fluid draining from the brain. If they detect the molecular calling cards of infection, cancer, or injury, they can mount an immune response.

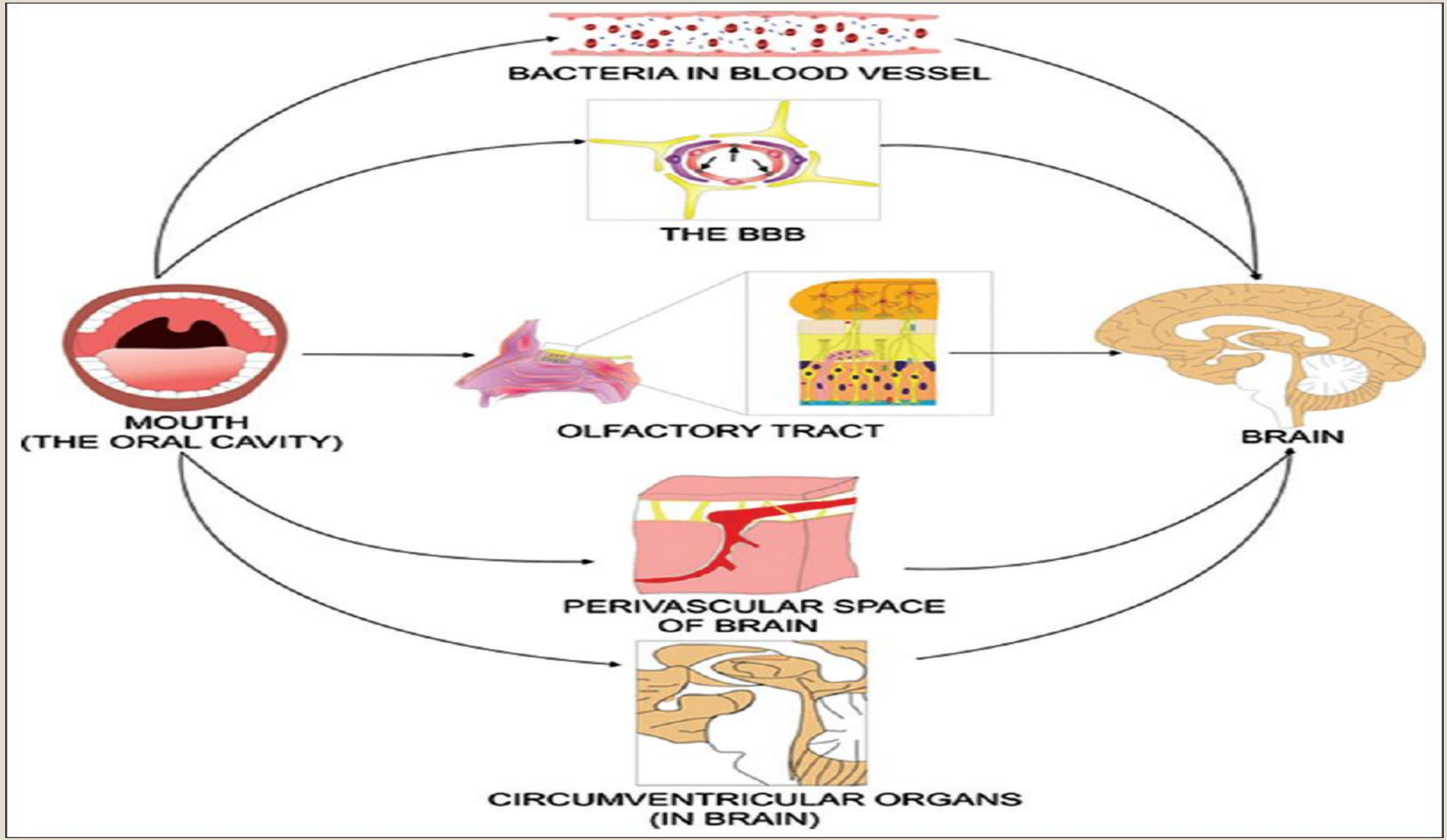
Immunity and the brain

- "Every organ in the body is being surveilled by the immune system," says senior author Dr. Jonathan Kipnis, Professor of Pathology and Immunology.

He explains:

"If there is a tumor, an injury, an infection anywhere in the body, the immune system has to know about it. But people say the exception is the brain; if you have a problem in the brain, the immune system just lets it happen. That never made sense to me. What we have found is that there is indeed immune surveillance of the brain — it is just happening outside the brain."

- **Microorganisms can enter into the brain by various means whether direct or indirect mechanisms and infect the brain.**
  - **In the direct mechanism, the mouth infects the olfactory tract, and the olfactory nerve carry the bacteria to the brain.**
  - **In other mechanisms, bacteria inside the mouth infect the blood and find their path via blood, blood brain barrier (BBB), perivascular spaces and circumventricular organs to reach the brain**


BACTERIA IN BLOOD VESSEL
THE BBB
MOUTH
(THE ORAL CAVITY)
OLFACTORY TRACT
BRAIN
PERIVASCULAR SPACE
OF BRAIN
CIRCUMVENTRICULAR ORGANS
(IN BRAIN)

◦Blood circulation

- In case of oral and periodontal diseases, the microbial-induced infection presents an extensive infectious burden to the entire body. Further, specific microorganisms within the microbial ecology associated with the disease process release toxins that invoke an inflammatory response.
- Bacteria, bacterial toxins, localized tissue response cytokines, and other inflammatory mediators enter the vascular circulation and can activate a systemic response. This entry into vascular channels happens through the gingival sulcus area, which harbors a high microbial load in periodontal diseases.

  Various dental treatments such as brushing, chewing, flossing, and use of tooth picks can also cause bacteraemia (a condition when there is bacteria in the blood) in a patient with periodontitis.
- This condition can occur several times in a day and is estimated to last approximately 3 hours for oral bacteria.
- Li reported bacteraemia in 100% post-dental extraction, 70% post-scaling, 55% post-third molar surgery, 20% post-endodontic treatment, and 55% post-bilateral tonsillectomy cases.
- Bacteraemia can be controlled by the immune system of the body; however, in subjects with a reduced immunity (the elderly patients), patients suffering from diabetes, rheumatoid arthritis, or malignancies, bacteria disseminate into the vascular channels. Within one minute after dissemination into vascular channels, bacteria may reach distant organs such as the heart, brain, lung, and peripheral blood capillaries

The blood–brain barrier

The **blood–brain barrier** (**BBB**) is a highly selective semipermeable border of endothelial cells that prevents solutes in the circulating blood from crossing into the extracellular fluid of the central nervous system where neurons reside.

All the blood capillaries of the body and brain have endothelial cells; however, these vascular endothelial cells of the brain differ from rest of the body vessels due to **the presence of tight junctions between them**. This nearly creates an impermeable boundary between the brain and the bloodstream

This system allows the passage of some small molecules by passive diffusion, as well as the selective and active transport of various nutrients, ions, organic anions, and macromolecules such as glucose and amino acids that are crucial to neural function.

The blood–brain barrier restricts the passage of certain harmful substances such as toxins and various bacterial pathogens, the diffusion of solutes in the blood, and large or hydrophilic molecules into the cerebrospinal fluid, while allowing the diffusion of hydrophobic molecules (O_2, CO_2, hormones) and small non-polar molecules.

The barrier also restricts the passage of peripheral immune factors, like signaling molecules, antibodies, and immune cells, into the CNS, thus insulating the brain from damage due to peripheral immune events.

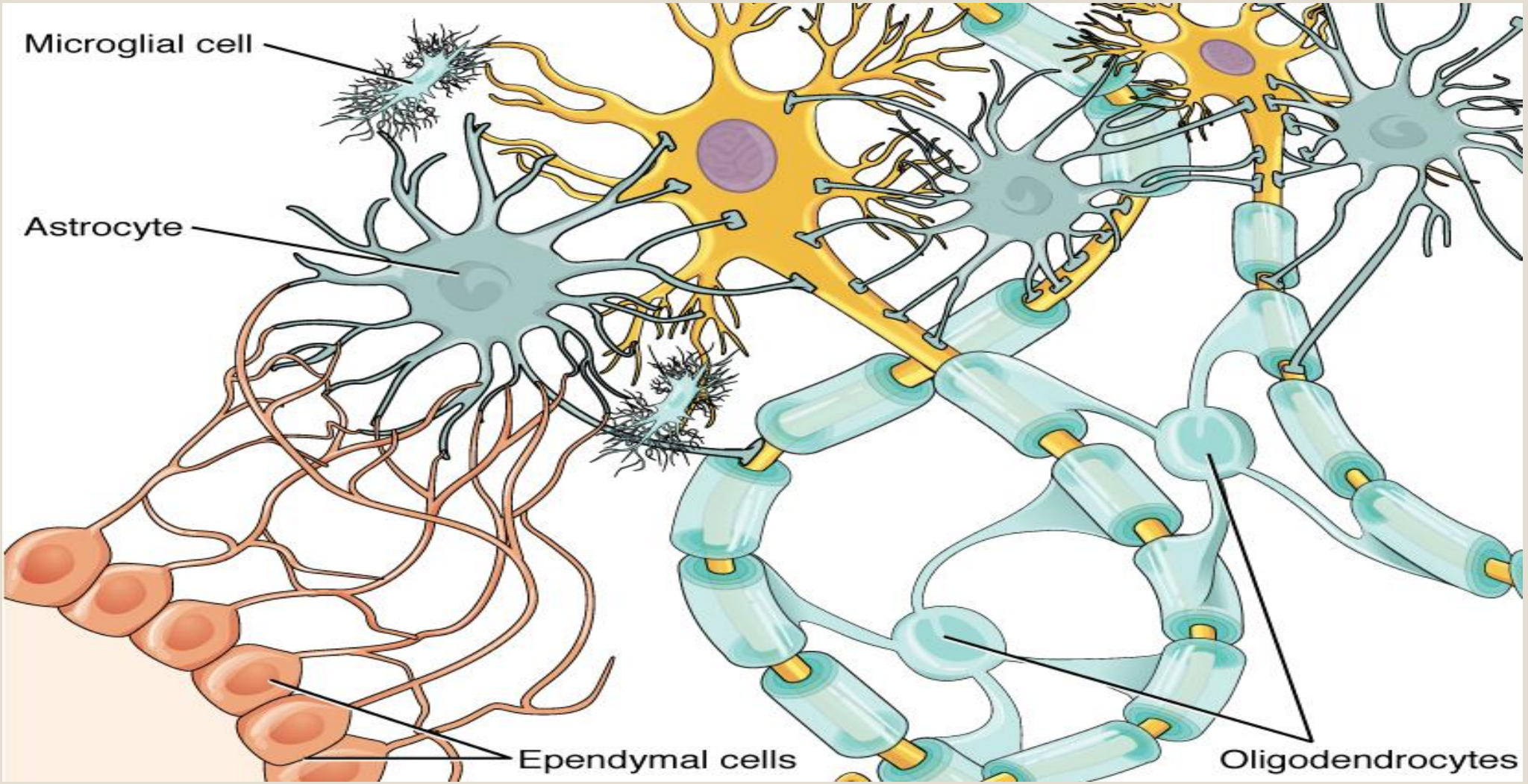
- The blood–brain barrier acts effectively to protect the brain from circulating pathogens. Accordingly, blood-borne infections of the brain are rare.
- Infections of the brain that do occur are often difficult to treat because Antibodies are too large to cross the blood–brain barrier, and only certain antibiotics are able to pass.
- In some cases, a drug has to be administered directly into the cerebrospinal fluid where it can enter the brain by crossing the blood-cerebrospinal fluid barrier.
- The blood–brain barrier may become leaky in certain neurological diseases, such as amyotrophic lateral sclerosis, epilepsy, brain trauma and edema, and in systemic diseases, such as liver failure.
- The blood–brain barrier becomes more permeable during inflammation, potentially allowing antibiotics and phagocytes to move across it. However, the aging process may favor the growth of oral microorganisms, mainly the anaerobic bacteria and facultative yeasts established in the early life, and may trigger proinflammatory responses that may weaken the BBB.[1]
- MRI confirmed that there is loss in the integrity of BBB in a mouse with candidiasis. This loss in integrity can allow the microorganisms to spread through the blood stream to the brain and thus may lead to neurodegeneration.

The Neuro-immune system

- Is a system of structures and processes involving the biochemical and electrophysiological interactions between the nervous system and immune system which protect neurons from pathogens.
- It serves to protect neurons against disease by maintaining selectively permeable barriers (e.g., the blood–brain barrier and blood–cerebrospinal fluid barrier), mediating neuroinflammation and wound healing in damaged neurons, and mobilizing host defenses against pathogens.
- The neuro-immune system and peripheral immune system are structurally distinct.
- Unlike the peripheral system, the neuroimmune system is composed primarily of glial cells which are considered as the key cellular components of the neuroimmune system, including astrocytes, microglia, and oligodendrocytes.

- Among all the hematopoietic cells of the immune system, only mast cells are normally present in the neuro-immune system and is naturally occur in the brain where they mediate interactions between gut microbes, the immune system, and the central nervous system as part of the microbiota–gut–brain axis.
- However, during a neuro-immune response, certain peripheral immune cells are able to cross various blood or fluid–brain barriers in order to respond to pathogens that have entered the brain.
- For example, there is evidence that following injury macrophages and T cells of the immune system migrate into the spinal cord. Production of immune cells of the complement system have also been documented as being created directly in the central nervous system

Different types of glial cells



Neuron-glial cell interaction

- Neurons and glial cells work in conjunction to combat intruding pathogens and injury.
- Chemokines play a prominent role as a mediator between neuron-glial cell communication since both cell types express chemokine receptors . For example, the chemokine fractalkine(Fkn) has been implicated in communication between microglia and dorsal root ganglion (DRG) neurons in the spinal cord.
- Fractalkine has been associated with hypersensitivity to pain when injected in vivo, and has been found to upregulate inflammatory mediating molecules.
- Glial cells can effectively recognize pathogens in both the central nervous system and in peripheral tissues. When glial cells recognize foreign pathogens through the use of cytokine and chemokine signaling, they are able to relay this information to the CNS.
- The result is an increase in depressive symptoms.
- **Chronic activation of glial cells however leads to neurodegeneration and neuroinflammation**.

- Microglial cells are of the most prominent types of glial cells in the brain. One of their main functions is phagocytosing cellular debris following neuronal apoptosis.
- Microglia and the complement system are also associated with synaptic pruning as their secretions of cytokines, growth factors and other complements all aid in the removal of obsolete synapses.
- Astrocytes are another type of glial cell that among other functions, modulate the entry of immune cells into the CNS via the blood–brain barrier (BBB).
- Astrocytes also release various cytokines and neurotrophins that allow for immune cell entry into the CNS; these recruited immune cells target both pathogens and damaged nervous tissue

Signalling cascade involved in microbe-induced neurodegeneration

- Bacterial infection, especially spirochetal infection, activates certain pathways, such as the integrin receptor-CR3 (CD11b/CD18), Toll-like receptor (TLR) signalling, and the complement cascade.
- The intermediate products of these pathways may be used as common markers of CNS inflammation. Spirochete-host interactions initiate and sustain the chronic inflammation, which trigger the immune responses, and later activate the innate and adaptive immune system, resulting in the production of free radicals, apoptosis, and amyloid deposition, which can be observed in AD brains.
- *P. gingivalis* is one the most important periodontal pathogens because it is capable of establishing and maintaining the periodontal disease associated "inflammophilic" microbiota.
- This bacteria is capable of performing this task as it possesses a variety of virulence factors that escape from the immune defence. Thus, *P. gingivalis* initially survives through sustainable inflammatory conditions and then attains nutrition by eliminating microbial competitors.

- *P. gingivalis* LPS and the presence of multiple lipid A structures makes the organism more difficult to be detected by the innate host responses and thus helps in sustaining the virulence of *P. gingivalis*.
- The possible outcome of finding of P. gingvalis LPS in the host brain include immune cell priming for the differential activation of TLR-facilitated NF-κB signalling pathway, which then leads to cytokine production, complement activation, and maintenance of intracerebral inflammation.
- Various reports suggested an imbalance in the synthesis and persistence of β-amyloid in the brain. The defective clearance of this protein in the brains of patients with AD leads to its accumulation in the form of insoluble Ab40/42 plaques.
- The increase in the antibody level in systemic circulation against bacteria may be considered as a diagnostic monitoring tool reflecting the clinical manifestations of neurodegenerative disorders.

- ## Circumventricular organs and perivascular spaces

  The circumventricular organs (CVO) are structures that allow polypeptide hypothalamic hormones to leave the brain without disturbing the BBB and permit substances that do not cross the BBB to trigger changes in brain function. The junctions of the capillary endothelial cells are not tight in the blood vessels of these regions compared to the BBB and may act as entry points to the brain for the bacteria. Perivascular spaces (PVS) are interstitial fluid-filled spaces that surround the perforated vessels and are most commonly located in the lower half of the basal ganglia. The systemic circulation through these spaces permit the bacteria and their products to find a direct access to the brain.

  ## The olfactory hypothesis

  The olfactory tract is the pathway through which the olfactory receptors send their electrical messages to the brain. This hypothesis states that the tract may possibly be a way for pathogens to approach the brain and thus may trigger the production of amyloid beta (Aβ) and neurofibrillary tangles (NFTs).The trigeminal and olfactory nerves were found to be used by several periodontal pathogens to approach the CNS, thus avoiding the BBB. The identification of oral treponemes in the trigeminal ganglia made researchers believe that it is a route for oral microorganisms to reach the brain.

- Olfactory ensheathing cells (OECs) engulf the bacteria and move towards the tumour necrosis factor-a (TNF-a) produced by activated astrocytes. Thus, OECs are also used as carriers for transporting live bacteria to the brain.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