**Physiol-13B4** Discuss the physiological significance of the blood-brain barrier.

**Definition**

The blood brain barrier (BBB) is the highly regulated interface that separates peripheral circulation and central nervous system

**Structure**

BBB consists of 3 layers:

Blood side
(1) endothelial cells (interconnected through *tight junctions*; no fenestrations)
(2) basal membrane (of both endothelial cells and astrocytes)
(3) astrocyte pedicles (foot processes)

CNS side

The layers contain various enzymes (e.g. MAO, AChE, etc) which degrade neurotransmitters → prevent their passage across BBB

The layers contain various transporters (e.g. GLUT-1, ion channels/pumps) → allow controlled passage of specific electrolytes, nutrients and drugs

**Neuroanatomy**

BBB separates almost the entire CNS from the peripheral circulation

However, the following CNS structures lie outside the BBB:

(1) *Area postrema* – a.k.a. chemoreceptor trigger zone; responsible for sensing noxious substances in the peripheral circulation → trigger nausea ± vomiting when detected
(2) *Organum Vasculosum Laminae Terminalis (OVLT)* – contains osmoreceptors directly in contact with peripheral circulation → sends signal to release ADH in response to ↑osmolality
(3) *Subfornical Organ (SFO)* – contains osmoreceptors as well as glucose sensors → senses energy state of the body
(4) *Posterior pituitary* – releases ADH and oxytocin into the circulation
(5) *Pineal gland* – responsible for regulating circadian rhythm via release of melatonin
(1), (2) and (3) above are circumventricular organs

**Permeability**

BBB is *permeable* to:

via passive diffusion/osmosis
- small molecules = \( \text{H}_2\text{O}, \text{O}_2, \text{CO}_2, \text{NH}_3, \) ethanol
- lipophilic substances = steroid hormones, lipophilic drugs \( \approx \) less than 30kDa

via active/facilitated transport
- glucose (GLUT-1 transporter)
- other hormones (e.g. insulin, thyroxine, etc)
- amino acids
- electrolytes (\( \text{Na}^+, \text{K}^+, \text{Ca}^{2+}, \text{HCO}_3^-, \text{Mg}^{2+}, \text{Cl}^- \))

BBB is usually *impermeable* to:
- large polar molecules
- large proteins (e.g. immunoglobulins)
- urea (very slow diffusion)
- bilirubin
- cells (e.g. leukocytes)

**Physiological Significance**

**(1) Protection**

BBB protects brain from endogenous and exogenous toxins in plasma
e.g. BBB leakiness in neonate \( \rightarrow \) brain exposed to unconjugated bilirubin (which is neurotoxic) \( \rightarrow \) kernicterus

**(2) Immunological barrier**

BBB protects brain from:
- pathogens in blood (damaged BBB \( \rightarrow \) encephalitis)
- the body’s immune system (damaged BBB \( \rightarrow \) autoimmune reaction to exposed CNS tissue; e.g. multiple sclerosis)

**(3) Maintain stable ionic environment in CNS**

BBB prevents free/rapid diffusion of ions \( \rightarrow \) maintains stable ionic environment in CNS, which is critical for normal neural transmission

BBB prevents rapid fluctuations in CNS [glucose] associated with meals \( \rightarrow \) prevents depletion of CNS nutrients (during hypoglycaemia) and glycosylation of neuronal tissue (during hyperglycaemia)

**(4) Maintain stable pH in CNS**

BBB prevents rapid diffusion of \( \text{H}^+/\text{OH}^- \) ions \( \rightarrow \) maintains stable CNS pH \( \rightarrow \) this is important in the regulation of respiration
**Mechanism**

CO₂ freely diffuses across BBB → dissociates to H⁺ and HCO₃⁻ → alters CSF pH
∴ medullary respiratory centre uses CSF pH as a surrogate marker for PaCO₂, which is a reflection of adequacy of ventilation

**(5) Barrier for neurotransmitters**

Prevents leaking of neurotransmitters out of CNS as well as prevents circulating neurotransmitters from affecting CNS neural circuits

**Situations of Altered BBB Function**

**Physiological**
Neonate – immature BBB

**Pathological**
Severe hypertension
Infection – meningitis
Seizure
Ischaemic stroke
Multiple sclerosis

**Examples of Anaesthetic Drugs**

**Antimuscarinics** – atropine penetrates BBB (tertiary amine), glycopyrrolate does not (charged quaternary amine)

**D₂ antagonists** – metoclopramide penetrates BBB (may precipitate EPSE), domperidone does not

**Examiner’s comments**

Candidates were expected to include a definition of the blood brain barrier (BBB) and the micro-anatomical features, unique to its function. The control of ion passage, along with which substances could freely pass and those which cannot was expected. Description of how the area postrema lies outside the BBB and the role in emesis was considered to be basic knowledge; better answers included other circumventricular organs and their role.

Many candidates incorrectly believed gap junctions to be present. Knowledge of neuroanatomy, and location of various physiological control centres within the brain was generally poor when specified in answers.

Most candidates correctly identified the role of the BBB in neuronal homeostasis, and the protective function against pathogens and toxins. Better answers included a barrier function separating central neurotransmitters from the periphery and vice versa, including descriptions of enzyme systems.
There was a wide variation in answers as to which ions were able to pass the blood brain barrier and which were not. Most candidates correctly identified the **impermeability to proteins**. The role of **carbon dioxide in altering CSF pH**, with ensuing stimulation of the respiratory centre was generally well understood when described. Many candidates discussed

Fick’s law of diffusion. Very few candidates were able to correctly interpret how it applied to the selective permeability of the BBB.

Many candidates also described the Monro-Kellie doctrine relating to intracranial pressure, which was not considered relevant to the actual question.

Better answers also included **situations of altered function of the BBB** (neonate, meningitis, profound hypertension etc). When describing particular properties of the BBB, examples of drugs (in particular those commonly used in anaesthesia) relating to those properties was useful.