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Relationship between neurological inflammation and debilitated blood brain barrier subsequent to General Anaesthesia

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Abstract
Recent advances in medicine have made it possible to successfully treat numerous disorders through surgical procedures, which frequently need the use of general anaesthetic. There is a rising interest in the CNS (central nervous system) issues related to anaesthetics, and concerns about the safety of general anaesthetic are on the rise as their usage becomes more commonplace. Recent years have seen a wealth of research pointing to the involvement of blood-brain-barrier (BBB) dysfunction and neurological inflammation in the emergence of CNS problems in the wake of anaesthesia. More research is needed to determine whether or not general anaesthesia causes BBB failure and neuroinflammation, and whether or not this interaction might be an option for treatment for CNS problems.

Keywords: Anaesthesia, blood–brain barrier, dysfunction; neuroinflammation, nervous system

Introduction

The development of anaesthetic methods and medications has been crucial to the steady improvement and fine-tuning of surgical practices over the past few decades. We feel the advancement of anaesthesia is one of medicine's greatest triumphs since it allows for long and difficult surgical procedures to be performed safely and reliably under general anaesthetic. By attaching to specific chemical receptors in the brain's nervous system (CNS), anaesthetics create a regulated, reversible loss of consciousness, creating the ideal environment for surgical procedures [1]. However, a rising body of research in recent years has called into question the safety of anaesthetics' widespread usage in clinical use. Numerous clinical and animal studies have suggested that certain anaesthetics may cause irreversible alterations in the structure and function of the central nervous system [2, 3, 4, 5]. The possible neurotoxicity of anaesthetic medications is becoming an increasing concern [6]. Recent years have seen an uptick in research on the correlation between neurocognitive impairment and neuroinflammation following general anaesthesia [7, 8, 9].

Inflammation is the body's normal protective response to harmful stimuli, but it may backfire if it's magnified above typical levels or gets out of hand. The brain, which is the organ of focus during general anaesthesia, may be more vulnerable to the systemic inflammatory response. As a natural immune defence system, neuroinflammation is crucial to keeping the brain's structure and functions normal, but it also plays a significant role in the development of neurodegenerative lesions and the death of neurons [10]. Inflammation in the brain and spinal cord has been identified as a hallmark of virtually every neurological illness [11, 12]. Inflammatory cytokines like interleukin-1 (IL-1) and cancer necrosis factor- (TNF-) have low basal expression levels in the CNS and are upregulated to varying degrees in response to infection, surgical excitement, or a stressful state [13].

A continuous layer of endothelial cells (ECs) linked by tight junctions, pericytes, the astrocytes microglia, and the surrounding basement membrane form a selective physical barrier called the blood-brain barrier (BBB) (Figure 1) that divides blood flow from the parenchyma of the brain and regulates the movement of substances between the central nervous system (CNS) and the periphery. Several neurological disorders, including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and stroke, have been linked to BBB dysfunction [14].

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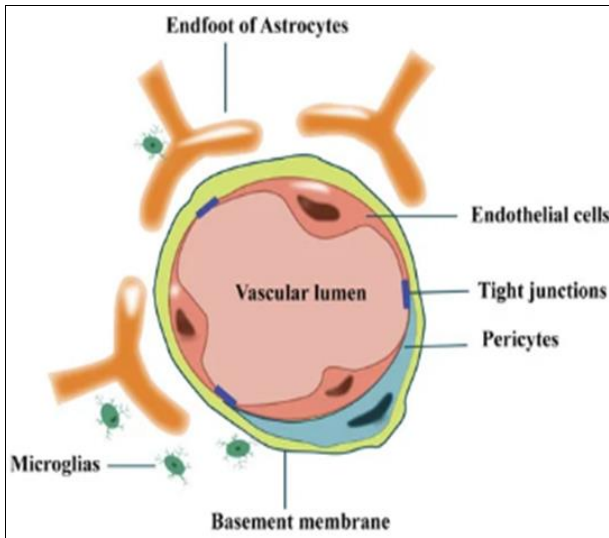Aljowhara Hospital Alain,
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Fig 1: Schematic diagram of the blood–brain barrier

In recent years, researchers' attention has been focused on the function of neuroinflammation in central nervous system (CNS) disorders related to anaesthesia. Targeted treatment of neuroinflammation is thought to reduce brain dysfunction following anaesthesia, although the mechanisms by which anaesthesia causes inflammation are still being studied. Numerous investigations [15, 16, 17, 18] have noted that anaesthetics used in clinical practice may compromise the BBB. Thus, it is clear that narcotic drug use is associated with neuroinflammation and BBB disruption, but the nature of the links between these two phenomena remains unclear. In this overview, we first provide a brief description of the BBB's function and structure, and then we investigate how inflammation impacts the BBB's key components. We then move on to talk about microglia, astrocytes, and their interactions, all of which have been linked to the emergence of neuroinflammation. Here, we review recent developments in our understanding of the neuroinflammation and BBB annihilation caused by frequently employed clinical anaesthetics, and we suggest future research directions and the possibility of improving CNS complications related to anesthetic-drug use through aimed suppression of neuroinflammation connected to BBB disorders.

The Blood–Brain-Barrier (BBB)
The Generation of BBB
An important part of the creation and maintenance of the CNS is played by the relationships among neuroectodermal endodermal cell precursors and their linked signal systems [19]. Embryonically formed blood vessels have endothelial tight junctions (TJs), nutrient carriers, a large number of transcellular vesicles, and high levels of leukocyte adhesion molecules; however, TJs grow more robust and intricate, transporters for efflux increase, and leukocyte attachment factors decrease only when close interaction has been established with cells and pericytes, which achieving both structural and functional maturation of the BBB [20, 21], Since the extracellular matrix is a dynamic component of the BBB that controls the structure and operation of the BBB by affecting cell-cell and cell-matrix interactions [13, 23], it increases endothelial-pericyte interactions and further increases pericyte binding on ECs, which are esophagolysosomal cells that secrete vesicles that transport

vesicles across the BBB. BBB function and integrity rely on the combined efforts of endothelial cells (ECs), pericytes (PCs), astrocytes (astrocytes), and the basement membrane (BM) that separates them all [26].

2.2 Endothelial Cells
The ECs are mesodermally derived altered squamous epithelial cells that assist create the vascular wall by adhering to the basement membrane [27]. Polarity in BBB ECs affects the directional transport of ions, chemicals, and immune cells form the bloodstream to the CNS [28], illustrating how the form and purpose of ECs on the BBB vary from those found in other tissues (Fig. 2). Also, compared to ECs from peripheral organs, BBB ECs have more mitochondria [29]. Paracellular transport is inhibited by the BBB's unique barrier property - the existence of TJs between ECs-while transcellular transport is hindered by the removal of fenestrations and lower transcytosis [30, 31]. Furthermore, BBB ECs have specialised transporters on the inside (such as the transporter for glucose protein 1) and the outside (such as P-gp (P-glycoprotein)) [14]. Several key adhesion molecules, including PECAM-1, triggered leukocyte cell adhesion molecule, ICAM-1, ICAM-2, CD99, and CD99-L2, were expressed and were involved in the migration of leukocytes on BBB ECs [32], while significant reduction of leukocyte adhesion molecule production in BBB ECs restricted the entry of immune cells into the CNS [33].
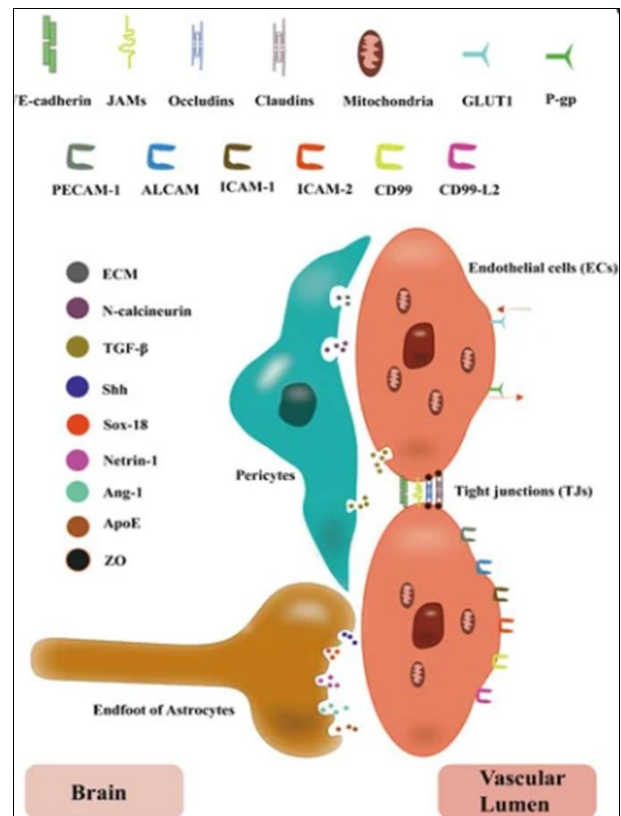

Fig 2: Structure and function of the main components of BBB

Moreover, vascular vascular calcium adhesin resides between ECs (Fig 2), where it regulates the shape, polarity, and the interior formation of ECs, plays a role in the upkeep of vascular integrity and permeability via intracellular indicate pathways and transcription variables, and protects ECs from apoptosis [34, 35].

2.3. Tight Junctions (TJs)

The BBB's distinctive barrier attribute is the presence of TJs between ECs [36]. TJs generate an asymmetry between the apical and basolateral membranes of ECs, which helps regulate paracellular permeability across the BBB [37]. Claudins, occludins, and junctional adhesive molecules (JAMs) are only a few examples of the many transmembrane proteins that make up TJs (Figure 2) [38]. Claudin-1, -3, -5, -11, and -12 are highly expressed in the central nervous system (CNS), while claudin-3, -5, and -12 are also found in brain ECs, where they contribute to the upkeep of BBB function [39]. The extracellular loop of occludins interacts with the band of ZO protein to create tight TJs, while the intracellular loop connects with the band of occludins [26]. The major JAMs expressed on TJs in the human BBB are JAM-A and JAM-C [40, 41], both of which are members of the CD2 group of the Ig superfamily. Leukocyte movement across the BBB may include BBB JAMs due to their ability to interact with integrin molecules found on the surface of different leukocytes, including T cells [42]. ZO protein, a multi-domain scaffold protein, links TJ proteins to the cytoskeleton [43]. Three PSD-95/discharge/Zonula occludens-1 (PDZ) domains, a src-homology-3 domain, and a guanylate kinase homology region are found at the N termini of ZO proteins [44]. PDZ-1 mediates the contact between ZO-1 and the C-terminus of claudins, while PDZ-2 and PDZ-3 mediate the interaction between ZO-1 and occludin and JAMs [45, 46].

2.4. A Brief History of the Pericytes

Capillary stability, diameter, brain blood flow, and extrinsic membrane protein release are all regulated by Pericytes, which are mesoderm-derived and line the central nervous system [13, 47]. TGF- is important in the regulation of the maintenance of BBB characteristics, and both the BBB ECs and their accompanying pericytes make TGF- and have functional TGF- receptors [48, 49]. Although the TGF- signal increases the synthesis of laminin and other extracellular matrix molecules in pericytes, it induces calbindin-2 (also known as N-calbindin) in BBB ECs to facilitate pericyte adherence (Figure 2) [50]. Detachment of the pericytes with the CNS vasculature, as well as an increase in BBB permeability and haemorrhage, might result from a faulty TGF- signal. Previous research suggested that the intimate relationship between BBB ECs and pericytes has a role in homeostasis maintenance and the control of trans-endothelial migration of leukocytes.

2.5. Astrocytes

Originating from radial glial cells, astrocytes are a prominent cell type in the central nervous system (CNS) that regulates BBB permeability by creating tight connections with the surface of CNS arteries via transmembrane anchoring proteins such -myotonic dystrophy protein and the aquaporin 4. Figure 2: Astrocytes are involved in the development and maintenance of the BBB barrier and

immunological function via autocrine signals. Secreted glycoprotein Shh participates in CNS-related morphogenesis in response to smoothing molecule-induced signals [22] by binding to the Patched-1 receptor on the surface of BBB ECs. claudin-5 expression is controlled by the secretion of Sox-18 in the BBB. A. c. The netrin-1 signal is produced to suppress CAM expression and control TJ molecule expression. d. The released Ang-1 stimulates angiogenesis, upregulates TJ molecules, and keeps the BBB stable by binding to the receptor tyrosine kinase Tie-2 on the surface of ECs. The secretion of lipoprotein particles containing apolipoprotein E (ApoE) contributes to the preservation of the BBB.

BBB and Inflammation

The BBB keeps a close eye on the surroundings and controls what can and can't enter the central nervous system (CNS), including inflammatory agents, cells, and other substances. BBB homeostasis is maintained by the epithelial and non-cellular elements performing their individual roles in conjunction with one another. Breakdown of the BBB can result from inflammation's effect on any of these factors. Increasing the openness of ECs and altering the ZO-1 cell-cell boundary are two primary ways in which BBB structure can be compromised by the production of pro-inflammatory cytokines or heightened pro-inflammatory responses. Recent investigations have shown that peripheral inflammatory factors can trigger the onset of neuroinflammation by entering the CNS following BBB breakdown. Since neuroinflammation is strongly linked to BBB instability, we will now examine the potential roles performed by the BBB's various components in the initiation and progression of neuroinflammation.

3.1 Neuroinflammation Often Occurs Due to Endothelial Cell Damage

Certain receptors and transporter on the surface of ECs allow for the direct transit of pro-inflammatory cytokines over the BBB and into the periventricular region of the BBB. Gram-negative bacteria's lipopolysaccharide (LPS) is employed as a model for systemic inflammation because of its immunogenic properties. Cell damage to the membrane, endoplasmic reticulum stress, and damage to mitochondria in BBB ECs, followed by apoptosis, were found to result from LPS's direct toxic effects. P-gp activity was found to be repressed, and matrix metalloproteinases were secreted in response to LPS. However, the inflammatory cytokine IL-1 may compromise the BBB by preventing ECs from properly adhering to their extracellular matrix and forming tight junctions. Activation and malfunction of BBB ECs in reaction to stimuli that are inflammatory are presently thought to be first steps in the onset of neuroinflammation, and we showed that inflamed can have especially severe impacts on ECs via various pathways. Since BBB failure is linked to neuroinflammation, EC disruption may be a crucial component in this chain.
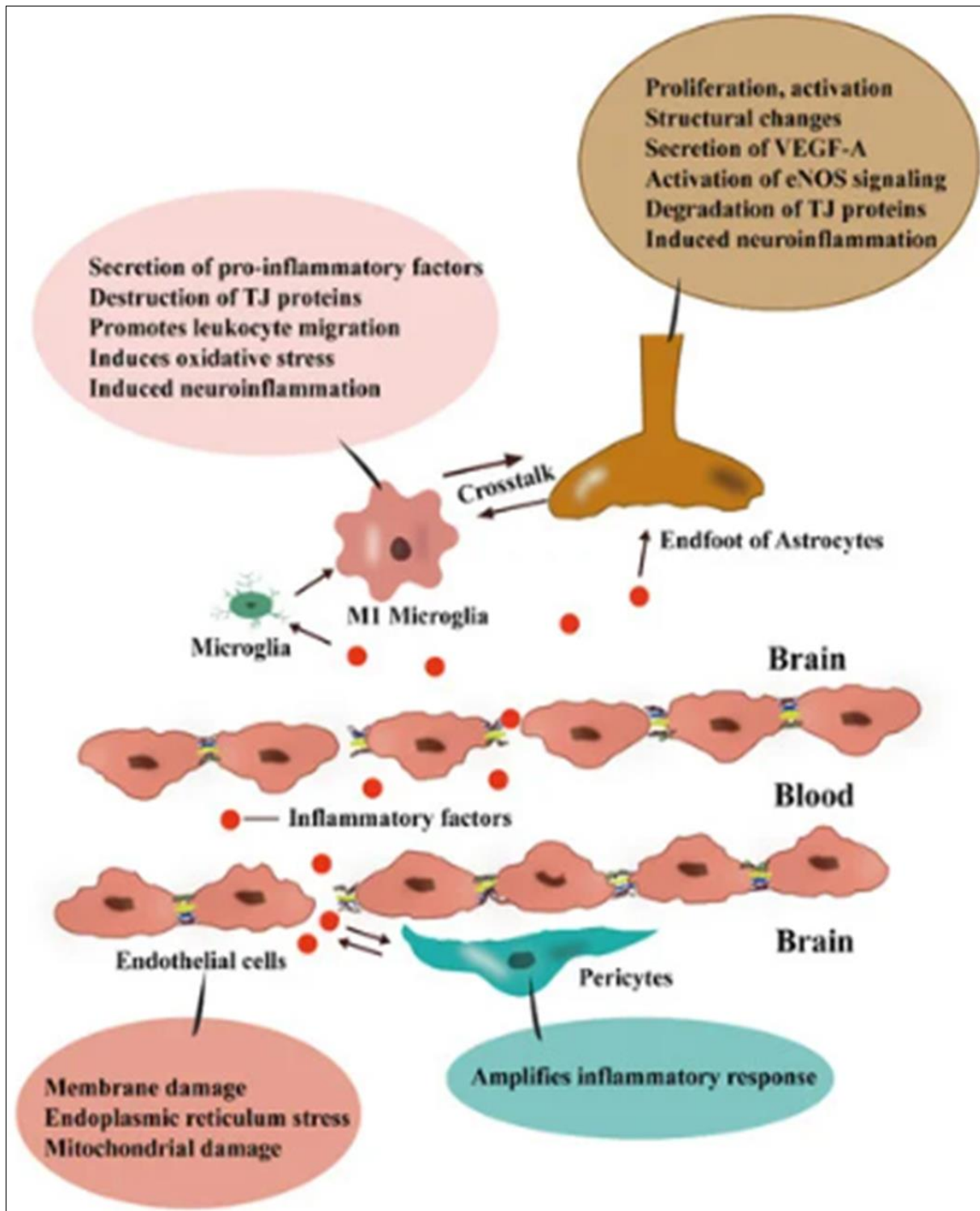
Fig 3: Schematic representation of BBB destruction due to inflammatory factors

3.2 Inflammation Disrupts the Components of TJs

Inflammatory factors including as IL-1, IL-6, IL-9, IL-17, IFN-, TNF-, and CCL2 have been linked to TJ degradation (Figure 3). Inflammation has been shown to cause claudin-5 degradation, reduction of claudin-5 expression, and uneven distribution across the plasma membrane of ECs, all of which further disrupt the BBB. In LPS-induced systemic inflammation, the occludin is degraded together with claudin-5, and a more recent research demonstrates that peripheral inflammatory cytokines decrease ZO-1 expression. According to the results of these investigations, an inflammatory condition has a significant impact on the BBB TJs and disrupts the BBB, resulting in dysfunction.

3.3 Increased Inflammation Due to Pericytes

In cocaine-mediated neuroinflammation, pericytes have been identified as a major source. Inflammatory mediators produced by pericytes have a function in maintaining the state of local inflammation. These mediators can increase the inflammatory response and control the movement of immune cells into the central nervous system. There is mounting evidence that pericytes contribute to BBB breakdown by increasing inflammatory responses (Figure 3). Therefore, we know that pericytes can further enhance neuroinflammation and lead to BBB breakdown when they detect inflammatory stimuli. In conclusion, inflammation may destroy the BBB by directly acting on its many

components, and it may also cause more neuroinflammation by impacting on the BBB itself. Pericytes primarily play a role in amplifying inflammation, while ECs are the primary targets of inflammation, which disrupts EC homeostasis and ultimately triggers apoptosis, then disrupts the relationships among ECs by halting the extracellular matrix and degraded the TJ proteins that lead to higher permeability of BBB. We shall explain why astrocytes (an essential part of the BBB) are left out of this discussion in the "Glial Cells and Neuroinflammation" section. The astrocytes and microglia will be discussed next.

4. Glia Cells and Neuroinflammation
Prolonged glial cell activation has been linked to synaptic depressive disorder and cognitive problems, neuroinflammation, and, in the end, neurodegeneration in the central nervous system. This activation is mediated primarily by astrocytes and microglia.

4.1 Astrocytes as Mediators between Peripheral Inflammation and Neuroinflammation
Astrocytes are the most numerous kind of glial cell in the central nervous system (CNS), and they play a crucial role in homeostasis maintenance and associated processes including immunological control via autocrine and paracrine signals. During the immunological trigger or inflammatory phase, astrocytes have been demonstrated to affect BBB permeability and the infiltration of peripheral immune cells. Proliferation, activation, and end-foot structural changes in astrocytes as well as other relevant gene expression variations can all be triggered by endotoxin-induced peripheral inflammation and contribute to BBB breakdown. By increasing VEGF-A secretion by astrocytes, activating the eNOS signal in ECs, and lowering expression of the tight junction proteins occludin and claudin-5, inflammatory substances can gain access to the CNS and set off neuroinflammation (Fig 3). The widely distributed astrocytic proteins S100 calcium-binding protein (S100) has been shown to play a neurotrophic or supportive role at low expression, but at high expression it has been shown to directly damage neurons, activate microglia and astrocytes, and induce receptive oxygen species (ROS) in microglia.

The aforementioned research demonstrates that inflammatory substances generated by peripheral tissues may also promote the growth of neuroinflammation via having detrimental effects on ECs and TJs via astrocytes, in addition to disrupting the BBB directly. The astrocyte protein S100 is probably a biomarker for the occurrence of neuroinflammation, and astrocytes could have a role in amplifying inflammation and acting as a centre of gravity for peripheral and neuroinflammation.

4.2 M1-Type Microglia Can Facilitate the Development of Neuroinflammation and Can also Disrupt the BBB
The brain's primary phagocytes, microglia, are responsible for eliminating infections and necrotic cells, cleaning up the environment, and preserving homeostasis. Toll-like receptor 4 (TLR-4) and other inflammatory signal receptors are upregulated in microglia in response to inflammation, which activates microglia and promotes the growth of CNS neuroinflammation, particularly in hippocampal tissue. Traditionally triggered M1 microglia and selectively activated M2 microglia have opposite effects on the brain, causing cell death in the former and protecting neurons in the latter.

Inflammatory cytokines, inducible nitric oxide synthase, nitric oxide, tumour necrosis factor alpha, reactive oxygen species, and interleukin (IL)-6 are only some of the pro-inflammatory chemicals that M1 microglia may create. Some research indicates that microglia that have been activated by inflammation can damage the BBB. Massive discharge of inflammatory cytokines exacerbates BBB damage and destruction through relationships with the BBB (Figure 3). These interactions include disruption of TJs activity, a rise in paracellular permeability, advancement of leukocyte migration, and stimulation of adsorptive endocytosis. Claudin-5 and occludin levels in the brain's microvasculature are lowered by IL-6. Production of nitric oxide and the subsequent generation of peroxynitrite by nitric oxide synthase reduces ZO-1 expression and heightens BBB leakage. The alternative is that reactive oxygen species (ROS) cause irreversible damage to cellular lipids, proteins, and DNA, leading to cell death and serving as a common trigger process for many subsequent processes that specifically target and damage the BBB, such as oxidative damage, strict junction modifications, and matrix metalloproteinase activation, thus disrupting BBB homeostasis.

However, M2 microglia phagocytose cellular debris and suppress the formation of inflammatory responses, aiding in the repair and lessening of BBB damage. Evidence suggests that M2 microglia can reduce BBB inflammation by producing anti-inflammatory cytokines such IL-10, IL-4, and IL-13. To prevent ROS from forming in ECs, IL-10 either downregulates enzymes that produce ROS or upregulates antioxidant pathways [109]. Both IL-4 and IL-13 limit the release of pro-inflammatory mediators such as IL-6, IL-1, TNF-, and ROS, while simultaneously promoting the phenotypic polarisation of M2 microglia.

Since M1-type microglia predominate during microglial activation, neuroinflammation is facilitated, and BBB homeostasis is disrupted; conversely, M2-type microglia predominate during microglial activation, protecting the central nervous system.

4.3 Crosstalk between Microglia and Astrocytes
The interaction between astrocytes and microglia is highly crucial, and it is interesting to note that neither astrocytes nor microglia function alone in the formation of neuroinflammation (Figure 3). Blocking CCR2 expression can reduce responses to inflammation in microglia and reverse the detrimental effects of neuroinflammation on cognitive performance. Astrocytes indirectly stimulate microglia by triggering microglial CCR2 overexpression via the CCL2-CCR2 signal pathway. However, microglia play a crucial role in astrocyte activation. Neurotoxic astrocytes can be produced from activated microglia via a chain of complements (C5, C3, and C1q). Microglia, according to recent research, can stimulate astrocytes as well. Hippocampal astrocyte activation produced by etomidate is attenuated over the long run if early microglia activation is eliminated. Microglia triggered by endothelial cells have been shown to have a distinct phenotype from microglia stimulated by astrocytes.

This data suggests that microglia and astrocytes communicate with one another, and that a "switch" mediates the trade-off amongst neurological inflammation and functional homeostasis in the brain.

5. Anaesthetics

In the past, it was believed that general anaesthetic was fully reversible and that although anaesthesia might produce substantial alterations in awareness, it did not leave persistent effects. Growing data suggests, however, that general anaesthesia is more than just a "immediate reversible condition" that has no lasting consequences on the central nervous system (CNS). Understanding the causes of central nervous system (CNS) issues associated with anaesthesia would allow for more precise therapy. Multiple investigations have shown that anaesthetics cause neuroinflammation and adverse CNS consequences by modulating microglia activation in a time-sensitive and dose-dependent manner. However, more investigations targeting the neurotoxicity of anaesthetics are required to elucidate the precise mechanism of neuroinflammation caused by general anaesthesia. We will then detail the ways in which specific clinical anaesthetics contribute to neuroinflammation and BBB malfunction.

5.1. Propofol

By binding to GABA-A receptors, the ultrashort-acting intravenous anaesthetic propofol increases Cl inward flow and hyperpolarizes neurons, rendering patients unresponsive to external stimuli. While a single dose of propofol has been shown to interfere with microglia operate and cause paradoxical behavioural. Manifestations in depressed mice, other studies have shown that propofol acts on glial cells, tampering with brain homeostasis and neuroinflammation and being linked to decreased neurocognitive function. Recent research has also linked propofol's severe neurotoxicity to the breakdown of the BBB as a result of inflammation and damage to ECs. Proteomic research results reveal that propofol can disrupt oxygen metabolism, damage to DNA detection, and stress response, all of which have implications for blood-brain barrier function. Propofol also causes an increase in BBB permeability [15] due to changes in resistance and permeability in exposed ECs. Long-term repercussions in adults from propofol's alteration of BBB permeability in the growing brain have also been hypothesised.

Although these studies have helped us gain a general understanding, the exact mechanisms and connections between propofol application and neuroinflammation and BBB disruption are still unclear, and further research into this topic is expected to help encourage perioperative brain function homeostasis.

5.2 Inhalation Anaesthesia

Inhaled anaesthetic medicines have been hypothesised to protect the brain by preventing BBB breakdown in earlier research. Recent research, however, has reached a different result. Brain homeostasis and neuronal function were disturbed in rats subjected to the inhaled anaesthetic sevoflurane because ECs had considerably flattened luminal surfaces, displayed age-related BBB degradation, and had impaired or disrupted BBB-associated tight junctions. Sevoflurane exposure, enhanced the BBB damage caused by surgical stimulation-induced reduction in occludin expression and rise in matrix metalloproteinase protein expression. In addition, high concentrations of isoflurane cause reversible concentration- and dependent on time morphological damage to the BBB ultrastructure, leading to an increase in BBB permeability. This occurs because the isoflurane causes a substantial reduction in tight junction protein occlusion protein expression and a rapid rise in membrane fluidity in various membrane systems. Sevoflurane inhalation anaesthesia has been linked to neuroinflammation in studies conducted during the past two years. It was discovered that sevoflurane caused neuroinflammation by preventing PI3K/Akt/mTOR pathway signal, and that neuroinflammation was suppressed and anaesthesia- and surgery-induced cognitive dysfunction were improved by infusing NAD-dependent deacetylase protein Sirtuin 3 into the hippocampus using a viral vector. Cognitive impairment following inhalation of sevoflurane is directly linked to neuroinflammation in the hippocampus, according to these results.

Overall, we found a strong correlation between inhaled anaesthetics and both BBB degradation and neuroinflammation; however, to far, no research have directly linked inhaled anesthetic-mediated BBB destruction to neuroinflammation. Is there a connection between these two, or do they mutually cause and amplify each other's effects? We think this is an intriguing subject, and further research is needed to fully understand the mechanisms at play.

5.3. Opioids

Opioids are frequently utilised in clinical anaesthesia because of their analgesic effects, which they do primarily via acting on the central nervous system. Since microglia include opioid receptors, it was shown that morphine causes a dose-dependent reduction in the survival of BV-2 microglia and mouse primary microglia via opioid receptors, leading to neuronal death. Furthermore, it was discovered *in vitro* that microglia's production of inflammatory cytokines was increased by LPS in the presence of morphine. TLR4-related myeloid differentiation factor-2 (MD2) is an innate immune receptor that opioids can bind to and alter microglia function. Adolescent rats treated to morphine showed a dramatic rise in microglial Toll-like receptor 4 (TLR4) mRNA and protein expression, which was strongly correlated with neuroinflammation. Female rats showed a higher sensitivity to morphine than male rats did when it came to morphine-mediated microglia TLR4 activation. Morphine causes inflammation and the release of inflammatory vesicles and NOD-like receptor protein 3 (NLRP3) in BV-2 microglia *in vitro*. Peter *et al*. also used pharmacological and genetic methods to determine that morphine causes the production of IL-1 and NLRP3 inflammatory vesicles in the spinal cord, both of which contribute to the development of chronic pain. Morphine keeps NLRP3 inflammatory vesicles activated in a positive feedback way by sustaining the release of damage-related molecular pattern. Furthermore, it has been established that opioids raise ROS concentrations, limit astrocyte formation, and result in cellular hypertrophy. It has been established that opiates like morphine can change tight junction expression of proteins, which in turn can cause BBB disruption. Opioid usage during clinical anaesthesia is closely linked to neuroinflammation, as has long been suspected. While microglial activation is responsible for this impact, it remains unclear whether opioid-derived neurological inflammation is linked to BBB breakdown.

5.4 Different α2-Agonists

α2-agonists are widely utilised in clinical anaesthesia because of their sedative, analgesic, bradycardic, hypotensive, and hypothermic actions. They do this by acting on widely expressed 2-adrenergic receptor in the central nervous system. In the central nervous system (CNS), 2-agonists have an anti-inflammatory and neuroprotective action, making them unique among anaesthetics. Dexmedetomidine (DEX), a common 2-agonist, impeded the generation and release of inflammatory mediators and cytokines in cultured microglia activated by LPS in a dose-dependent manner, including iNOS or NO, IL-1, and TNF, while also preventing microglia activation and improving microglia phagocytosis. In addition, miRNA-mediated anti-inflammatory and neuroprotective properties of DEX have been shown in a number of different tests. Apoptosis of hippocampal neurons, DNA injury, neuroinflammation, and reduced cognitive impairment have all been linked to DEX-induced upregulation of miRNA-381 and inhibition of the Egr1/p53 pathway in mice under sevoflurane anaesthesia. These effects are antagonistic in various pathological models of neuroinflammation, ischemia-reperfusion injury, and anesthetic-induced neurotoxicity. Negatively regulating the BBB, miR-155 is essential in BBB-associated neuroinflammation. Time-dependent increase of miRNA-155 expression in the hippocampus, brain, and plasma was seen during LPS-induced neuroinflammation and was greatly decreased by DEX therapy.

Evidence from the literature suggests that beta 2-agonists have neuroprotective benefits via many pathways, and we point out that these effects may be linked to the BBB's ability to dampen down neuroinflammation. However, no appropriate research have been conducted to verify this link. To further investigate these possibilities and add to perioperative brain homeostasis, further research is needed in the future.

6. Conclusions and future directions

In the "Anaesthesia" section, we reviewed the effects on neuroinflammation and BBB function of certain regularly used perioperative anaesthetic medications, including propofol, inhaled anaesthetics, opioids, and 2-agonists. Several anaesthetics were shown to have a strong correlation with the emergence of neuroinflammation and BBB disruption, with the exception of 2 agonists, which had a beneficial impact. We reviewed only a few of the most widely used anaesthetics and restrict us to the consequences of a single medication, despite the fact that in clinical practise, numerous types of anaesthetics are typically employed in a precise order. Animal and cell studies, in which the simultaneous administration of various medicines might have varying results, were the other primary sources we considered. Additional research on the impact of various anaesthetics on neurological inflammation and BBB function in medical settings is required.

In animal and cellular investigations, a single injection of propofol, inhalation anaesthetics, and opioids can cause neuroinflammation and BBB disruption. The interaction between neuroinflammation and BBB failure was previously described. However, no research have yet shown whether or how BBB impairment and neuroinflammation induced by anaesthetic medications interact with one another. The novelty of this article is that it bridges the gap between neuroinflammation and BBB malfunction, which in turn gives fresh insights into the essential role of anaesthetics and opens up interesting new discoveries and opportunities for investigating CNS problems linked with general anaesthesia.

Conflict of Interest

Not available

Financial Support

Not available

References

1. Moody OA, Zhang ER, Vincent KF, Kato R, Melonakos ED, Nehs CJ, *et al*. The Neural Circuits Underlying General Anesthesia and Sleep. Anesth. Analg. 2021;132:1254–1264.
2. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: Mechanisms and relevance. Nat. Rev. Neurosci. 2016;17:705–717.
3. Fodale V, Tripodi VF, Penna O, Fama F, Squadrito F, Mondello E, *et al*. An update on anesthetics and impact on the brain. Expert. Opin. Drug. Saf. 2017;16:997-1008.
4. Liu X, Ji J, Zhao GQ. General anesthesia affecting on developing brain: Evidence from animal to clinical research. J. Anesth. 2020;34:765–772.
5. Zhao X, Hao LJ, Zhang YT, Zhang Y, Zhang C. Influence of general anesthetic exposure in developing brain on cognition and the underlying mechanisms. Sheng Li Xue Bao. 2019;71:749–759.
6. Fodale V, Ritchie K, Rasmussen LS, Mandal PK. Anesthetics and Alzheimer's disease: Background and research. J Alzheimer's Dis. 2010;22(S3):1–3.
7. Lin H, Kang Z, Li S, Zeng J, Zhao J. Sarm1 is Essential for Anesthesia-Induced Neuroinflammation and Cognitive Impairment in Aged Mice. Cell Mol. Neurobiol. 2022;42:1465–1476.
8. Li Q, Zhang X, Li S, Li W, Teng Y, Zhou Y, *et al*. Carnosol alleviates sevoflurane-induced cognitive dysfunction by mediating NF-kappaB pathway in aged rats. Drug Dev. Res. 2022;83:1342–1350.
9. Peng L, Liu S, Xu J, Xie W, Fang X, Xia T, *et al*. Metformin alleviates prolonged isoflurane inhalation induced cognitive decline via reducing neuroinflammation in adult mice. Int. Immunopharmacol. 2022;109:108903
10. Daiello LA, Racine AM, Yun Gou R, Marcantonio ER, Xie Z, Kunze LJ, *et al*. Postoperative Delirium and Postoperative Cognitive Dysfunction: Overlap and Divergence. Anesthesiology. 2019;131:477–491.
11. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimer's Dement. 2016;12:719–732.
12. El Idrissi F, Gressier B, Devos D, Belarbi K. A Computational Exploration of the Molecular Network Associated to Neuroinflammation in Alzheimer's Disease. Front. Pharmacol. 2021;12:630003.
13. Zheng Z, Chopp M, Chen J. Multifaceted roles of pericytes in central nervous system homeostasis and disease. J Cereb. Blood Flow Metab. 2020;40:1381–1401.
14. Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron.

2008;57:178–201.

15. Hughes J, Neese O, Bieber D, Lewis K, Ahmadi L, Parsons D, *et al*. The Effects of Propofol on a Human *in vitro* Blood-Brain Barrier Model. Front. Cell. Neurosci. 2022;16:835649.

16. Spieth L, Berghoff S, Stumpf S, Winchenbach J, Michaelis T, Watanabe T, *et al*. Anesthesia triggers drug delivery to experimental glioma in mice by hijacking caveolar transport. Neuro-Oncol. Adv. 2021;3:140.

17. Zhang Q, Zheng M, Betancourt C, Liu L, Sitikov A, Sladojevic N, *et al*. Increase in Blood-Brain Barrier (BBB) Permeability Is Regulated by MMP3 via the ERK Signaling Pathway. Oxidative Med. Cell. Longev. 2021;2021:6655122.

18. Acharya N, Goldwaser E, Forsberg M, Godsey G, Johnson C, Sarkar A, *et al*. Sevoflurane and Isoflurane induce structural changes in brain vascular endothelial cells and increase blood-brain barrier permeability: Possible link to postoperative delirium and cognitive decline. Brain Res. 2015;1620:29–41.

19. Langen UH, Ayloo S, Gu C. Development and Cell Biology of the Blood-Brain Barrier. Annu. Rev. Cell Dev. Biol. 2019;35:591–613.

20. Ma S, Kwon HJ, Huang Z. A functional requirement for astroglia in promoting blood vessel development in the early postnatal brain. PLoS ONE. 2012;7:e48001.

21. Nakamura K, Ikeuchi T, Nara K, Rhodes CS, Zhang P, Chiba Y, *et al*. Perlecan regulates pericyte dynamics in the maintenance and repair of the blood-brain barrier. J. Cell Biol. 2019;218:3506–3525.

22. Alvarez JI, Dodelet-Devillers A, Kebir H, Ifergan I, Fabre PJ, Terouz S, *et al*. The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. Science. 2011;334:1727–1731.

23. Shimizu F, Kanda T. Pericytes of the Nervous System: Physiological and Pathological Role. Brain Nerve. 2020;72:151–158.

24. Reed MJ, Damodarasamy M, Banks WA. The extracellular matrix of the blood-brain barrier: Structural and functional roles in health, aging, and Alzheimer's disease. Tissue Barriers. 2019;7:1651157.

25. Augustin HG, Koh GY, Thurston G, Alitalo K. Control of vascular morphogenesis and homeostasis through the angiopoietin-Tie system. Nat. Rev. Mol. Cell Biol. 2009;10:165–177.

26. Sanchez-Cano F, Hernandez-Kelly LC, Ortega A. The Blood-Brain Barrier: Much More Than a Selective Access to the Brain. Neurotox. Res. 2021;39:2154–2174.

27. Sigaud R, Dussault N, Berenguer-Daize C, Vellutini C, Benyahia Z, Cayol M, *et al*. Role of the Tyrosine Phosphatase SHP-2 in Mediating Adrenomedullin Proangiogenic Activity in Solid Tumors. Front. Oncol. 2021;11:753244.

28. Sonar SA, Shaikh S, Joshi N, Atre AN, Lal G. IFN-gamma promotes transendothelial migration of CD4 (+) T cells across the blood-brain barrier. Immunol. Cell Biol. 2017;95:843–853.

29. Hermann DM, El-Ali, A. The abluminal endothelial membrane in neurovascular remodeling in health and disease. Sci. Signal. 2012;5:re4.

30. Harilal S, Jose J, Parambi DGT, Kumar R, Unnikrishnan MK, Uddin MS, *et al*. Revisiting the blood-brain barrier: A hard nut to crack in the transportation of drug molecules. Brain Res. Bull. 2020;160:121–140.

31. Lee MJ, Jang Y, Han J, Kim SJ, Ju X, Lee YL, *et al*. Endothelial-specific Crif1 deletion induces BBB maturation and disruption via the alteration of actin dynamics by impaired mitochondrial respiration. J Cereb. Blood Flow Metab. 2020;40:1546–1561.

32. Daneman R, Zhou L, Agalliu D, Cahoy JD, Kaushal A, Barres BA. The mouse blood-brain barrier transcriptome: A new resource for understanding the development and function of brain endothelial cells. PLoS ONE. 2010;5:e13741.

33. Vestweber D. Adhesion and signaling molecules controlling the transmigration of leukocytes through endothelium. Immunol. Rev. 2007;218:178–196.

34. Giannotta M, Trani M, Dejana E. VE-cadherin and endothelial adherens junctions: Active guardians of vascular integrity. Dev. Cell. 2013;26:441–454.

35. Shao Y, Chen J, Freeman W, Dong LJ, Zhang ZH, Xu M, *et al*. Canonical Wnt Signaling Promotes Neovascularization through Determination of Endothelial Progenitor Cell Fate via Metabolic Profile Regulation. Stem Cells. 2019;37:1331–1343.

36. Liu B, Li Y, Han Y, Wang S, Yang H, Zhao Y, *et al*. Notoginsenoside R1 intervenes degradation and redistribution of tight junctions to ameliorate blood-brain barrier permeability by Caveolin-1/MMP2/9 pathway after acute ischemic stroke. Phytomedicine. 2021;90:153660.

37. McConnell HL, Mishra A. Cells of the Blood-Brain Barrier: An Overview of the Neurovascular Unit in Health and Disease. Methods Mol. Biol. 2022;2492:3–24.

38. Cong X, Kong W. Endothelial tight junctions and their regulatory signaling pathways in vascular homeostasis and disease. Cell. Signal. 2020;66:109485.

39. Liebner S, Fischmann A, Rascher G, Duffner F, Grote EH, Kalbacher H, *et al*. Claudin-1 and claudin-5 expression and tight junction morphology are altered in blood vessels of human glioblastoma multiforme. Acta Neuropathol. 2000;100:323–331.

40. Leon-Rivera R, Veenstra M, Donoso M, Tell E, Eugenin EA, Morgello S, *et al*. Central Nervous System (CNS) Viral Seeding by Mature Monocytes and Potential Therapies To Reduce CNS Viral Reservoirs in the cART Era. mBio. 2021;12:e03633-20.

41. Nagasawa K, Chiba H, Fujita H, Kojima T, Saito T, Endo T, *et al*. Possible involvement of gap junctions in the barrier function of tight junctions of brain and lung endothelial cells. J Cell. Physiol. 2006;208:123–132.

42. Hartmann C, Schwietzer YA, Otani T, Furuse M, Ebnet K. Physiological functions of junctional adhesion molecules (JAMs) in tight junctions. Biochim. Biophys. Acta Biomembr. 2020;1862:183299.

43. Tornavaca O, Chia M, Dufton N, Almagro LO, Conway DE, Randi AM, *et al*. ZO-1 controls endothelial adherens junctions, cell-cell tension, angiogenesis, and barrier formation. J Cell Biol. 2015;208:821–838.

44. Fanning AS, Anderson JM. Zonula occludens-1 and -2 are cytosolic scaffolds that regulate the assembly of cellular junctions. Ann. N. Y. Acad. Sci. 2009;1165:113–120.

45. Itoh M, Furuse M, Morita K, Kubota K, Saitou M,

Tsukita S. Direct binding of three tight junction-associated MAGUKs, ZO-1, ZO-2, and ZO-3, with the COOH termini of claudins. J Cell Biol. 1999;147:1351–1363.

46. Ebnet K, Schulz CU, Meyer Zu Brickwedde MK, Pendl GG, Vestweber D. Junctional adhesion molecule interacts with the PDZ domain-containing proteins AF-6 and ZO-1. J. Biol. Chem. 2000;275:27979–27988.

47. Beazley-Long N, Durrant AM, Swift MN. Donaldson, L.F. The physiological functions of central nervous system pericytes and a potential role in pain. F1000Research. 2018;7:341.

48. Ten Dijke P, Arthur HM. Extracellular control of TGFbeta signalling in vascular development and disease. Nat. Rev. Mol. Cell Biol. 2007;8:857–869.

49. Antonelli-Orlidge A, Saunders KB, Smith SR, D'Amore PA. An activated form of transforming growth factor beta is produced by cocultures of endothelial cells and pericytes. Proc. Natl. Acad. Sci. USA. 1989;86:4544–4548.

50. Hill J, Rom S, Ramirez SH, Persidsky Y. Emerging roles of pericytes in the regulation of the neurovascular unit in health and disease. J Neuroimmune Pharm. 2014;9:591–605.