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*Review Article*

# Postoperative delirium

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## Introduction

Delirium is one of the common complications after surgeries, systemic inflammation is thought to be a driver for postoperative delirium, usually as a result of the surgery. Furthermore, complex surgeries are typically linked to greater rates of postoperative delirium [1]. Perhaps the kind of operation can affect how delirium develops [2]. Longer procedures put patients at higher risk for intraoperative hypoxemia.

Although the exact pathophysiologic cause of delirium is still unknown, it can be thought of as the last common pathway that results from several causes that combine to cause a state of impaired brain activity [3].

Despite the fact that delirium has been observed in patients of different age groups and those undergoing various surgeries, aging has been recognized as an important risk factor for postoperative delirium [4]. At present, the rapid progress of population aging is undoubtedly a major challenge we are facing. Recent concerning research findings show that elderly patients who experience delirium or cognitive impairment after surgery are three times more likely to develop permanent cognitive impairment or dementia compared to other patients [5].

Therefore, exploring the potential mechanisms of postoperative delirium and seeking effective treatment methods and drugs have become important issues that need to be addressed urgently.

Here, we reviewed the process by which postoperative peripheral inflammation develops into neuroinflammation and ultimately leads to postoperative delirium, as well as its underlying mechanisms.

### Surgical trauma and peripheral inflammation

Surgical operations will inevitably cause tissue damage, thereby triggering the body's activation of the immune system and initiating an inflammatory response. However, an excessive inflammatory response not only poses a risk of damaging the patient's tissues and organs but also can lead to complications such as postoperative delirium [6]. In addition, anesthetic drugs can also induce the occurrence of inflammation [7].

### Damage-associated molecular patterns

Damage-Associated Molecular Patterns (DAMPs) are immunostimulatory molecular patterns in sterile inflammation, associated with tissue damage, and are distinguished from pathogen-associated molecular patterns (PAMPs) [8]. The latter are mainly induced by exogenous pathogens such as bacteria, viruses, and fungi. However, both of these patterns can initiate an inflammatory response through the same cellular Pattern Recognition Receptors (PRRs) [6].

DAMPs are not only released from damaged cells but can also be actively secreted by the stress response of some cells. After being released into the intercellular space, they will bind to cellular PRRs and exert their functions [9].

The known PRRs include Toll-Like Receptors (TLRs), G Protein-Coupled Receptors (GPCRs), NOD-Like Receptors (NLRs), and RIG-I-Like Receptors (RLRs). The activation of most of these receptors can induce an inflammatory response, leading to the production of cytokines and chemokines [10]. For example, TLR2 and TLR4 can recognize endogenous proteins and glycoproteins in the Extracellular Matrix (ECM) and promote the activation of NF-κB and MAPK [11]. The activation of NF-κB will lead to changes in the patterns of transcription and release of cytokines.

The pro-inflammatory effect of DAMPs highly depends on the expression of specific PRRs on the cell surface. Among them, NLRP3 is regarded as the most important receptor for sensing DAMPs, because it can sense a variety of DAMPs. For example, oxidized mitochondrial DNA and histones can directly activate the NLRP3 inflammasome. Even lipid metabolites can induce the activation of NLRP3 through the classical pathway mediated by ROS [12].

The pro-inflammatory activity of DAMPs depends on various factors. For example, changes in concentration: Compared with normal cells, damaged cells will secrete more proteoglycans, which act as ligands to bind to TLRs and activate the inflammatory response [12].

**Changes in location:** DNA is mainly located in the nucleus and mitochondria, and nucleotides are protected from detection by the immune system. When cells are damaged, it leads to the release of DNA, which is detected by DNA sensors and activates the immune response [13]. Changes in nature: The degradation products of high-molecular-weight hyaluronic acid can activate TLR2 and TLR4 [14].

In summary, DAMPs encompass various types of molecules, including nucleic acids, proteins, glycoproteins, lipids, and metabolites. This implies that even in seemingly simple manifestations of inflammation, the coordinated action of multiple types of DAMPs is often involved, rendering the pathological mechanisms extremely intricate.

## Macrophage

As highly plastic immune cells, macrophages are widely distributed in various tissues and organs and play a variety of different roles during the perioperative period, such as removing foreign substances, promoting or inhibiting inflammation, accelerating tissue remodeling, and facilitating scar formation [15].

Macrophages are usually divided into two subgroups, M1 macrophages and M2 macrophages, and their functions are different from each other. M1 macrophages can release cytokines including IL-12, IL-1β, IL-6, TNFα and inducible Nitric Oxide Synthase (iNOS), and are involved in the release of inflammatory cytokines and the generation of Th1-type responses to enhance the bactericidal activity of macrophages [16]. M2 macrophages release anti-inflammatory factors such as IL-10 and IL-1RA to mediate the resolution of inflammation. Moreover, they promote angiogenesis by releasing growth factors such as PDGF, VEGF, and EGF, so as to accelerate wound healing [17].

The local cytokine environment can guide the polarization of macrophages. Among them, DAMPs are most closely associated with surgical procedures. In addition, PAMPs, INF-γ, and TNF can all induce the polarization of macrophages into the M1 type, while IL-4, IL-10, and TGF-β can induce the polarization of macrophages into the M2 type [18]. The polarization direction depends not only on the types of cytokines but also on the amount of cytokines and the exposure time. For example, some T cells can simultaneously produce Interleukin-4 (IL-4) and Interferon-γ (INF-γ), which respectively drive the polarization towards the M2 type and the M1 type [19].

## Change in mast cells

Mast cells are present in most tissues and are mainly located in areas close to the external environment, such as the skin, respiratory tract, and gastrointestinal tract. Relying on their advantageous location, they become one of the earliest cells to appear in the inflammatory response [20].

Mast cells can be activated in a variety of ways. In addition to the classic cross-linking of the high-affinity receptor (FcεRI) with IgE molecules, there is also the binding of complement and toll-like receptors and the ligation of Mas-related G protein-coupled receptor member X2 (MRGPRX2) [21]. After mast cells are activated, degranulation occurs, which involves the fusion of the granule membrane with the plasma membrane, and preformed mediators will be released extracellularly within a few minutes [22], including proteases, histamine, cytokines (such as TNF-α, IFN-γ, IL-1, IL-6, etc.), and growth factors, and thus participate in the inflammatory response [23]. Mast cells may be potential sensors of neurotransmitters secreted by nerve endings, because they are closely located to the surrounding nerve endings and also express a variety of neurotransmitter receptors, such as neurokinin 1 receptor and calcitonin receptor-like receptor [24].

The study by JC Ansel et al. provided some evidence that the neuropeptide substance P released by sensory fibers can selectively activate the expression of TNF-α mRNA in mouse mast cells, thus promoting the secretion of TNF-α [25].

The functions of mast cells are not confined to peripheral inflammation. They are also distributed around the blood vessels and nerves in the Central Nervous System (CNS), Hongquan Dong et al. discovered that inhibiting the degranulation of brain mast cells can prevent the activation of microglia and alleviate inflammation in the central nervous system [26].

Mast cells can disrupt the BBB by reducing tight junction proteins such as occludin and claudin-5. They can also indirectly disrupt the BBB by upregulating MMP-2 and MMP-9 [27].

### Peripheral – central nervous system immune interaction

Inflammatory mediators outside the central nervous system can enter the central nervous system through multiple pathways, promoting neuroinflammation [28]. For example, by adhering to the BBB endothelial cells, leading to disruption of cell-cell adhesions and increased endothelial permeability [29]; Through areas in the brain where there is no complete blood - brain barrier, like the circumventricular organs (CVO) [30]; Transportation occurs across the intact BBB via transporters [31], The peritoneal cavity and the brain stem can communicate directly according to the vagus nerve's sensory afferent fibers [32].

## Blood - brain barrier

The BBB plays a vital role in the protection and function of the brain. It separates the circulating blood from the extracellular fluid of brain cells, maintaining a stable environment in the brain [33]. It allows the selective passage of nutrients and molecules essential for brain function while preventing the entry of potentially neurotoxic substances [34].

Pericytes, glial cells (microglia and astrocytes), Brain Microvascular Endothelial Cells (BMECs), and a basement membrane make up the intricate, multicellular Blood-Brain Barrier (BBB) [35]. The BMECs are the central component of this assembly, and they are closely linked by Adherent Junctions (AJs), Gap Junctions (GJs), and Tight Junctions (TJs).

Pericytes express a variety of adhesion molecules, especially Intercellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1). This helps pericytes mediate the migration and crawling of white blood cells into the gaps covered by the endothelium [36]. In the absence of pericyte-mediated action, most white blood cells will be cleared by the perivascular drainage pathway in the perivascular region [37]. Some studies have found that pro-inflammatory factors can cause the morphological changes of pericytes [38]. Under the combined action of these factors, white blood cells can breach the blood-brain barrier more efficiently.

There are various ways to affect the permeability of the BBB. For example, promoting structural changes in capillaries, causing pericyte atrophy, and abnormal accumulation of laminin in the basement membrane can increase the permeability to small molecules and plasma proteins and enhance the migration of immune cells [39].

Changes in the BBB during systemic inflammation can be divided into disruptive and non-d isruptive types.

**Disruptive BBB change**

Claudin-5 is the main cell-adhesion molecule of tight junctions in brain endothelial cells and plays an important role in size-selective loosening of the Blood-Brain Barrier (BBB). Experiments by Takehiro Nitta et al. showed that claudin-5-deficient mice all died shortly after birth, and it was found that the BBB of these mice had selective permeability to small molecules (<800 D) [40].

After surgery, the activation of plasminogen will occur, and subsequently, the permeability of the Blood-Brain Barrier (BBB) will be increased through the generation of bradykinin mediated by plasmin and the subsequent activation of bradykinin B2 receptors [41].

Thrombin-induced PAR1 activation increases the cytoplasmic $Ca^{2+}$ concentration in cerebral blood vessels, leading to nitric oxide release and an increase in F-actin stress fibers, which disrupts the integrity of the BBB [42].

In various states of peripheral inflammation, leukocytes adhere to the endothelial cells of the blood - brain barrier. This leads to the disruption of cell adhesion and an increase in endothelial permeability [43].

The research by Mashhood A. Sheikh et al. discovered that peripheral inflammation can lead to an increase in sICAM-1, enabling leukocytes to migrate along the BBB vasculature and ultimately reach the perivascular space. There, the leukocytes secrete inflammatory signals, further promoting neuroinflammation [44]. In addition, sICAM-1 can cause MIP-2 to be released in mouse astrocytes and brain microvascular endothelial cells, which leads to neuroinflammation [45].

Imaging techniques have revealed changes in the structure and function of the BBB during the pathogenesis of Alzheimer's Disease (AD) [46]. This supports the idea that the BBB in a diseased state is more sensitive to systemic inflammation than in a healthy state [47].

**Non-disruptive BBB change**

Vascular endothelial cells and pericytes specifically express Solute carrier family 22 member 8 (Slc22a8). Research indicates that the downregulation of Slc22a8 expression induced by Middle Cerebral Artery Occlusion/Reperfusion (MCAO/R) may be one of the key mechanisms underlying the alteration of BBB permeability [48].

Research has shown that the neurotransmitter glutamate promotes the release of messengers such as prostaglandin E and nitric oxide. These messengers help to dilate capillaries by actively relaxing pericytes and then regulate blood flow [49].

After surgery, the activation of plasminogen will occur, and subsequently, the permeability of the Blood-Brain Barrier (BBB) will be increased through the generation of bradykinin mediated by plasmin and the subsequent activation of bradykinin B2 receptors.

Exosomes can cross the blood-brain barrier from the periphery to the central nervous system [50]. Moreover, studies have found that there are astrocyte-specific proteins released in exosomes in rat blood, which confirms the ability of exosomes to travel from the central nervous system to the peripheral circulation [51]. Of course, the specific effect on the BBB depends more on the content of exosomes. For example, neurons release exosomes containing miR-13, leading to an upregulation of the expression of TJ (VE-cadherin) and thus enhancing the integrity of the BBB [52]. Astrocytes regulate the properties of the BBB through crosstalk with BMECs by releasing paracrine factors [53].

## Circumventricular organs

Circumventricular organs, including the Subfornical Organ (SFO), Organum Vasculosum of the Lamina Terminalis (OVLT), and area postrema, occupy a unique position within the central nervous system. What sets them apart is their location outside the Blood - Brain Barrier (BBB) [30].

CVOs are important brain regions for detecting peripheral inflammatory signals.

It seems that the Circumventricular Organs (CVOs) have remarkable characteristics compared with other parts of the brain. The lack of tight junctions between their endothelial cells leads to the formation of pores, through which macromolecular cytokines carried in the blood can enter the central nervous system. Moreover, a special structure called the Virchow - Robin spaces slow down the flow rate of blood through the CVOs, facilitating the diffusion of molecules in the blood [54].

Many previous reviews on neuroinflammation only regarded CVOs as a kind of passageway. However, each of the CVOs contains a high density of receptors for a large number of different circulating signals. These signals play a crucial role in signaling the autonomic state from the periphery to the central nervous system.

**Subfornical organ (SFO)**

The subfornical organ (SFO) is located on the roof of the third ventricle, behind the column of the fornix and attached to the terminal plate vein. It lacks the blood-brain barrier, which enables it to directly contact various substances in the circulatory system [55].

cGAS serves as a molecular sensor for damaged mitochondria and is present in the endothelial cells of the SFO. Free mitochondrial DNA (mtDNA) in the peripheral circulation can activate cGAS after entering the endothelial cells of the SFO [56,57]. Similarly, Dihydroorotate Dehydrogenase (DHODH), a mitochondrial redox regulator, directly interacts with cGAS in endothelial cells, facilitating cGAS activation [58]. cGAS not only regulates the production of type I interferons and inflammatory cytokines via the classical STING pathway, but also significantly promotes the generation of Reactive Oxygen Species (ROS), resulting in oxidative cell damage [59], which impacts neuroinflammation within the brain.

Research shows that the p55 TNF - α receptor and the IL - 1 receptor accessory protein (a subunit of the IL - 1 receptor) are densely distributed in the SFO. These data suggest that the SFO is a major site in the brain where circulating pro - inflammatory cytokines elicit a sympathetic nerve response [60].

**Organum vasculosum of the lamina terminalis (OVLT)**

Numerous studies indicate that the OVLT plays a crucial role in the fever - induction pathway during inflammation. It can activate the genome of brain cells through inflammatory transcription factors such as STAT3 and IL6, regulating the transcription of key terminal inflammatory target genes involved in the fever response [61,62].

Polyunsaturated Fatty Acids (PUFAs) are highly abundant in the central nervous system. These lipids serve as precursors to a large number of lipid metabolites, which are crucial for the occurrence of brain inflammation and the communication between the activated immune system and the brain during systemic inflammation [63].

Some research has pointed out that several lipids increase or decrease in the OVLT during cerebral inflammation, indicating that it plays a role in the signal transduction between peripheral and central immunity [64].

In the experiment by Lois M. Harden et al., it was shown that the release of pro-inflammatory factors from OVLT-cultured cells pretreated with IL-10 antibody increased significantly [65].

**Area postrema (AP)**

The area postrema is a medullary structure located at the floor of the fourth ventricle.

## Vagus nerve

The Vagus Nerve (VN) is the longest nerve in the human body and is distributed in most organs which serves as a vital conduit between the brain and peripheral organs and is a significant part of the parasympathetic nervous system. Peripheral inflammatory chemicals are sensed by afferent vagus nerve fibres, which then send signals to the brain [66]. The anti-inflammatory effect of the vagus nerve is mediated through multiple pathways, which we will list in the following text.

Borovikova et al. found that by stimulating the abdominal vagal afferent fibers, the release of pro-inflammatory factors such as Tumor Necrosis Factor (TNF), Interleukin (IL)-1β, IL-6, and IL-18 could be inhibited, but the release of the anti-inflammatory cytokine IL-10 would not be affected [67].

The α7 nicotinic acetylcholine receptor (α7nAChR) plays a crucial role in the process by which acetylcholine released from the vagus nerve endings inhibits macrophage activation [68]. The use of the α7 nicotinic acetylcholine receptor agonist GTS - 21 to attenuate the production of TNF-α also illustrates this point [69]. The α7nAChR mediates the JAK2/STAT3 signaling pathway, thus reducing the production of inflammatory cytokines [70].

There are IL-1β receptors on the vagus nerve afferents. These receptors transmit information to the Nucleus of the Solitary Tract (NTS). Neurons located in the A2 noradrenergic group are activated and then project information to the parvocellular region of the Paraventricular Hypothalamus (PVH) around neurons containing Corticotropin-Releasing Factor (CRF). Then, these CRF neurons activate the pituitary gland to release adrenocorticotropic hormone and ultimately stimulate the adrenal glands to release glucocorticoids to reduce peripheral inflammation [71].

The stimulation of the vagus nerve can suppress the activation of coagulation and fibrinolysis in rats during endotoxemia [72], safeguarding the integrity of the BBB by means of this inhibition [42].

## Neuroinflammation

Neuroinflammation is one of the characteristics of postoperative delirium.

The central nervous system relies on glial cells, particularly microglia and astrocytes, for immune surveillance and response to various neuropathological injuries.

Initiating an adaptive T cell-mediated immune response in the CNS is much more difficult than in the periphery. For example, the survival of foreign tissue grafts within the CNS parenchyma is prolonged. Similarly, the injection of bacteria or adenovirus does not trigger a pro-inflammatory T-cell response in the CNS parenchyma [73]. This may be related to the inability of microglia and astrocytes to present antigens to T cells [74].

These glial cells are classified into neurotoxic/pro - inflammatory M1 microglia and A1 astrocytes, as well as anti - inflammatory/neuroprotective M2 microglia and A2 astrocytes.

Chronic neuroinflammation can induce the generation of pro-inflammatory M1 microglia and A1 astrocytes.

Microglia and astrocytes can communicate in both directions throughout the inflammatory process, with each cell type utilising cytokines, chemokines, and other signalling molecules to specify the other's immunological activity [75].

There is a vicious cycle formed by the interaction between reactive astrocytes and microglia, leading to the production of more pro-inflammatory factors and reactive oxygen species, which further exacerbates neuroinflammation.

**Microglia**

Microglia are the resident immune cells in the CNS and play the role of macrophages in the brain. They are responsible for eliminating microorganisms, dead cells, redundant synapses, protein aggregates, and other particulate and soluble antigens that may endanger the CNS [76]. However, they possess not only immune pro-inflammatory functions but also protective functions, which makes their roles in neurological diseases paradoxical. For instance, in Alzheimer's disease, on one hand, microglia help to clear amyloid deposits and release growth factors to support synaptic remodeling [77]. On the other hand, they can promote the hyperphosphorylation of tau protein and

cause neuronal loss through the release of inflammatory factors [78].

Microglia are also involved in the process from peripheral inflammation to neuroinflammation by acting on the Blood-Brain Barrier (BBB). In the early stage of systemic inflammation, microglia migrate to the BBB, express tight junction proteins such as Claudin-5, maintain its integrity, and come into contact with endothelial cells. In the late stage of systemic inflammation, microglia become reactive and start to phagocytose essential components of the BBB and the end-feet of astrocytes, leading to increased trans-barrier permeability and the infiltration of systemic inflammatory factors [79].

Microglia express cell receptors such as Toll-Like Receptors (TLRs), nucleotide oligomerization domain-like receptors, and viral receptors, which can recognize Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs) [80]. After being stimulated, microglia produce inflammatory factors to promote neuroinflammation.

The activity of microglia is regulated by pro-inflammatory and anti-inflammatory cytokine receptors. These cytokines are either produced by glial cells within the Central Nervous System (CNS) or reach the CNS from the circulation, such as IFN-α/β (30), IFN-γ, TNF-α, IL-1β, IL-10, and TGF-β.

Microglia can activate astrocytes through multiple pathways, further exacerbating neuroinflammation. For example, microglia release pro-inflammatory cytokines such as IL-1α, TNF-α, and C1q, which can induce astrocytes to develop a neurotoxic phenotype. Alternatively, they can induce the transformation of astrocytes into the A1 phenotype by downregulating the CXCR7/PI3K/Akt signaling pathway [81].

**Astrocytes**

As the most numerous glial cells in the CNS, astrocytes play a crucial role in controlling the innate and adaptive immune responses inside the CNS [82].

Astrocytes are not only involved in the maintenance and permeability of the BBB, but also provide metabolites and growth factors for neurons, support synapse formation and plasticity, and regulate the extracellular balance of ions, fluids, and neurotransmitters. Therefore, they are crucial for brain homeostasis [83].

Astrocytes play a complex role in neuroinflammation. This is because reactive astrocytes can be classified into at least two distinct subtypes: neurotoxic A1 and neuroprotective A2 [84]. A1 reactive astrocytes produce excessive inflammatory cytokines and reactive oxygen species, leading to neuronal cell death and the disruption of neural circuits [75].

The induction of A1 astrocytes often requires the participation of reactive microglia [85]. Interestingly, complement component 3 (C3) is one of the most typical and highly upregulated genes in A1 astrocytes [86]. Moreover, astrocytes can promote the activation of microglia through the complement-related pathway (C3-C3aR) [87]. The feed-forward inflammatory cycle existing among these central nervous system cells may be the cause of the overproduction of inflammatory factors and the occurrence of delirium.

Furthermore, the transition of astrocytes from a resting state to a reactive state significantly reduces their support for normal synaptic function [88]. Research shows that every synapse in the CNS is enveloped by at least one astrocyte, and a single astrocyte may have processes projecting to hundreds of synapses [89,90]. This astrocyte-neuron interaction is crucial for regulating synaptic transmission to ensure the normal activity of neural circuits.

**Neurons**

Neurons have often been regarded as victims of immune attacks. However, research has found that they do not merely passively participate in the immune response of the CNS [91].

For example, microglia and astrocytes express low levels of MHC and costimulatory molecules and can hardly activate naive T cells efficiently, thus leading to T cell anergy [92,93].

However, neurons can express MHC class I molecules after being stimulated by interferon (IFN)-γ [94], which makes it possible for neurons to control cellular immunity. Moreover, studies have shown that soluble neuronal factors, including cytokines, neuropeptides, neurotrophic factors and neurotransmitters, can attenuate the activation of microglia and T cells [95,96].

Through the mediation of the neural cell adhesion molecule NCAM, neurons can inhibit the production of nitric oxide and the pro-inflammatory cytokine Tumor Necrosis Factor (TNF) by Lipopolysaccharide (LPS)-stimulated glial cells [97], thereby reducing neuroinflammation.

Not only NCAM, but also many neuronal membrane glycoproteins such as CD22, CD47, CD200, and the neural cell adhesion molecule CD56, have been shown to prevent microglial activation through interaction with their respective counter-receptors [98-100].

An increasing number of studies suggest that neurons can participate in the CNS immune response. 1. After neuronal damage, neurons can regulate the immune response by releasing damage-associated molecular pattern molecules. For instance, High-Mobility Group Box 1 (HMGB1), a nuclear protein within the DAMP molecules, promotes the innate immune response by binding to Toll-Like Receptors (TLR) and Receptors for Advanced Glycation End-products (RAGE) [101]. 2. Neurons may induce the apoptosis of T cells or microglia by expressing Fas ligand (FasL, CD95L). The FasL-Fas pathway provides neurons with a mechanism to restrict harmful immune responses [102]. 3. Healthy neurons constitutively express high levels of the chemokine CX3CL1. Through CX3CL1-CX3CR1 signal transduction, the activity of neurotoxic microglia is inhibited [103]

## Consequences of neuroinflammation

**Amyloid-β deposition**

Aβ is produced through the sequential cleavage of Amyloid Precursor Protein (APP) by β-secretase and γ-secretase, mainly existing in two forms: Aβ40 and Aβ42. Generally, it is believed that Aβ42 is more prone to aggregation than Aβ40. Therefore, Aβ42 is considered to be a more potent form in amyloidogenesis and neurotoxicity [104].

The aggregation of Aβ monomers will form oligomers, which will then polymerise into insoluble fibrous precipitates, thus hindering neuronal communication and affecting memory and cognitive functions [105]. Under normal physiological conditions, microglia can effectively intervene in Aβ deposition through phagocytosis, forming a barrier around the plaques, and the enzymatic degradation of Aβ [106]. However, the acti-

vation of microglia is closely related to the increased Aβ burden [107]. With the excessive activation of neuroinflammation, the conversion of microglia into the M1 phenotype will lead to a decrease in the phagocytic and degradation abilities of microglia.

The binding of Aβ to the complement component C1q can activate the classical complement pathway, leading to excessive phagocytosis of synapses by microglia [108]. The study by Hong et al. found that inhibiting the expression of C1q, C3, and C3R can effectively reduce the number of activated microglia and early synaptic loss [109].

The study by Paouri et al. found that the deficiency of TNF-α can reduce Aβ in the brain. TNF-α can affect the production of Aβ by decreasing the levels of β-secretase and α-secretase in the mouse brain [110]. Conversely, Aβ can also induce an inflammatory response, leading to the production of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [111].

Amyloid-β can activate the JNK signaling pathway via WNT5A-ROR2 to reduce synapse formation [112]. It can also lead to the dysfunction of NMDA-type glutamate receptors and reversible synaptic loss through the mGluR1- and AKAP150-anchored calcineurin signaling pathway [113]. Moreover, the accumulation of β-amyloid protein can enhance oxidative stress and result in mitochondrial dysfunction and energy failure [114].

The increase in Aβ levels after surgery can trigger the neuropathological processes that are considered to be the basis of delirium, such as neuroinflammation and synaptic dysfunction [115]. Moreover, the elevated Aβ levels after surgery may accelerate the long-term development of Aβ-related conditions, increasing the risk of dementia in patients who experience postoperative delirium [116].

**Synaptic dysfunction**

Synapses are the basic structural and functional components of neural communication in the brain. They possess a high degree of variability and plasticity, and are also extremely sensitive to pathological conditions. The disruption of the structure and function of synapses may be the main determinant for the occurrence of neurological symptoms.

The ability of mitochondria to rapidly buffer calcium during intense stimulation is essential for synaptic plasticity. Synaptic transmission also relies on ATP to maintain and restore the ionic gradient [117]. However, neuroinflammation can damage mitochondria, affecting their functions of producing ATP and regulating the local intercellular calcium concentration.

The basic functions of glial cells are crucial for maintaining synaptic activities. For example, astrocytes not only physically eliminate synapses through the MEGF10 and MERTK pathways [118], but also participate in synaptic plasticity relying on the close physical connections between their processes and synapses. Moreover, the processes of astrocytes are highly dynamic and can continuously adjust their degree of association with synapses [119]. Thrombospondins 1-5 (TSP1-5) and hevin derived from astrocytes induce the formation of structurally excitatory synapses, and the secreted Glypican 4 and 6 also have the same effect [120]. Microglia prune synapses depending on the receptors CX3CR1 and CR3. For instance, the Complement Receptor 3 (CR3) binds to C3, which may mark the less active synapses and target them for elimination [121]. In addition, animal experiments have found that the loss of Brain-Derived Neurotrophic Factor (BDNF) in microglia will lead to a decline in the learning ability of mice [122]. It is worth noting that synaptic dysfunction will reduce the production of neurotrophic factors [123].

As already mentioned, neuroinflammation will prompt astrocytes to transform into neurotoxic A1 type and microglia to transform into neurotoxic M1 type, thus affecting the normal synaptic function.

**Oxidative stress**

The Reactive Oxygen Species (ROS) in the brain mainly originate from the mitochondria within neurons and glial cells. However, this conclusion is only applicable under physiological conditions. Under pathological conditions, mitochondria actually generate fewer free radicals than enzymes such as NADPH oxidase in the cytoplasm [124]. Under natural conditions, the human body maintains a balance between oxidation and antioxidation. The increased production of ROS may cause the redox balance of cells to tip towards an oxidative state, leading to cell dysfunction and even death [124]. Among various types of ROS, the hydroxyl radical (·OH) is regarded as the most reactive and is capable of inducing cytotoxic effects [114].

Oxidative stress leads to mitochondrial dysfunction by altering the mitochondrial membrane potential, nitrating mitochondrial proteins, decreasing the activity of the mitochondrial electron transport chain, and causing a loss of neuronal biogenesis [126].

ROS can cause oxidative modification of cellular macromolecules such as lipids, proteins, and DNA. For example, it can catalyze lipid peroxidation, leading to an increase in the fluidity of the cell membrane, the loss of membrane-protein activity, and the disruption of the integrity of the cell membrane [127]. Proteins related to energy metabolism, chaperone proteins, and the ubiquitin-proteasome system are often more sensitive to oxidation [128]. Moreover, a variety of proteins have been proven to be inactivated during oxidative stress, and even the antioxidant protein Sod1 is no exception [129]. This may lead to a vicious cycle, further exacerbating oxidative stress.

Proteins damaged by oxidative stress should be degraded by the proteasome. However, oxidative stress may damage the protease system responsible for removing oxidized macromolecules, accelerating the formation of protein aggregates [128]. And these protein aggregates may be highly cytotoxic [130].

Cells can utilize ROS/RNS as signaling molecules to participate in neural responses. For example, neurons in the central nervous system can sense and transmit ROS signals [131]. However, at high concentrations of ROS, synaptic neurotransmission will be weakened, which is related to the modification of target protein receptors (such as ERK, PKC, and CREB) through redox reactions [132].

ROS may stimulate the activation of microglia by activating p38 and c-Jun N-terminal kinase (JNK) [133].

## Concluding remarks and future perspectives

From surgical operation to postoperative delirium, we recognize that the development of inflammation is closely associated with postoperative cognitive dysfunction. Although inflammation is essential for tissue repair, an uncontrolled inflammatory response can severely impact the prognosis of patients. Searching for methods to block inflammation or potential targets has always been a research focus. For instance, lipoxin A4 (LXA4) in-

hibits neuroinflammation and oxidative stress by increasing the expression of SIRT1 and reducing the protein level of acetylated NF-κB p65 [134]. Triggering receptor expressed on myeloid cells 2 (TREM2) improves neuroinflammation by promoting the expression of sirtuin 3 in BV2 cells [135]. However, these mechanisms still require further investigation.

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