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Review

Cognitive Change Associated with Anesthesia and Surgery: An Introduction to POCD for Neuroscientists

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Abstract

Postoperative cognitive dysfunction (POCD) is a central nervous system (CNS) complication seen in elderly patients, characterized by a decline in memory, comprehension, and attention in patients after surgery and general anesthesia. The pathophysiologic mechanisms of postoperative cognitive dysfunction are not well understood and effective means of prevention and treatment are currently lacking. Basic and clinical research, including the use of pre-clinical animal models of POCD, is advancing rapidly. In this paper, we review and summarize various factors that contribute to the development of POCD, including oxidative stress, autophagy, impaired synaptic function, and neuroinflammation, and describe the construction of animal models of POCD. By analyzing the gap between clinical and basic research, we propose recommendations for clinically relevant animal model development and the conducting of clinical studies to better understand the mechanisms and etiology associated with POCD. We aim to enhance understanding of the occurrence of POCD and to provide a more comprehensive perspective on the prevention and treatment of POCD.

Keywords: postoperative cognitive dysfunction; oxidative stress; autophagy disorders; impaired synaptic function; neuroinflammation; cognitive change

1. Introduction

Postoperative cognitive dysfunction (POCD) is a common neurological complication following surgery and general anesthesia [1], especially in elderly patients. Postoperative cognitive dysfunction seriously affects patients' quality of life, prolongs hospitalization, and creates a heavy burden on society [2]. However, the etiologic and pathophysiologic mechanisms that trigger POCD warrants further research. As the population ages, the use of anesthesia in the geriatric surgical population is increasing. POCD is a new type of cognitive impairment that occurs after anesthesia and surgery, a complication characterized by impaired memory, decreased information processing, and decreased attention, which can be detected weeks to months after surgery and may be long-lasting [3]. Although a common complication of the central nervous system after surgery in elderly patients, it is often accompanied by a range of negative outcomes, such as mood and personality changes [3,4]. Data from a prospective trial in a non-cardiac surgery population showed that the prevalence of POCD was as high as 30% [5]. According to a study by Brown *et al.* [6], patients who developed delirium after surgery experienced declines in multiple cognitive domains at one month and were more likely to develop POCD.

According to the available research, the occurrence and development of POCD are associated with various factors. Among them, neuroinflammation is considered to play a crucial role in the pathogenesis of POCD and has become an important research topic in recent years. Animal and human studies have shown that surgical or anesthesia-induced neuroinflammation is a major cause of POCD development [7,8]. Surgery-induced tissue damage activates the peripheral immune system and promotes an inflammatory response leading to neuroinflammation and degeneration [9]. The severity and duration of POCD are the result of several factors and therefore develop in different directions in different individuals [10]. The underlying pathophysiologic mechanisms of POCD remain unclear, and preventive or ameliorative therapies are lacking. The effectiveness of several pharmacologic and nonpharmacologic interventions based on current hypothesized mechanisms is still under investigation. Although POCD is a CNS disorder, the research on them is predominantly conducted by anesthesiologists rather than neuroscientists. The purpose of this review is to introduce POCD to a wide range of scientists and to facilitate communication between anesthesiologists and neuroscientists. Here, we first review the development history of POCD and then summarize key analyses to elucidate its mechanism for animal model development. Secondly, based on the existing research and evidence, we analyze the important mechanisms potentially involved in the pathogenesis of POCD. By summarizing the clinical studies on POCD and comparing them with the basic research, we can provide suggestions for future exploration.

2. The History of POCD

POCD is a well-known surgical risks and was described as a "side effect" of anesthesia as early as 1887 [11]. Altered cognitive function in patients after anesthesia and surgery has been on physicians' radar for over a hundred years. American dentist Zacheus Rogers was committed to a mental hospital in 1872 for nerve damage caused by nitrous oxide abuse [12]. At that time, it was widely recognized that infections and patients' "somatic susceptibility" might be associated with changes in patients' postoperative cognition [13]. At the time, reports of "insanity" and "death" from the use of anesthetics were on the rise throughout the United States [13]. In 1887, the American dentist Samuel J Hayes published a report linking anaerobic anesthetics to ventricular respiration and insanity, followed by a report on cases of insanity by the British psychiatrist George H. Savage [12]. Neuropathologist Cyril B. Courville published two articles on asphyxiating brain injury in 1936 [14,15]. POCD attracted the attention of the medical community many years ago, but the causes and mechanisms of postoperative cognitive changes have not been well-studied. In 1955, Bedford first reported a series of neurological complications, such as impaired orientation and amnesia in elderly people with no preoperative abnormalities [4]. After the 1980s, multiple studies utilized detailed neuropsychological tests to assess cognitive changes after cardiac surgery [16–18]. The study found a decline in cognitive function in older patients after anesthesia and surgery, yet it was more than seven years before changes in cognitive function were detected [16]. In 1998, the International Study Group on Postoperative Cognitive Dysfunction (ISPOCD) conducted a multicenter study that formally introduced POCD, a study with important implications for understanding and intervening in postoperative cognitive dysfunction [19]. Since then, the medical community has begun to conduct research into the clinical manifestations, incidence, and other aspects of POCD. An early study found that the incidence of POCD was relatively high after major operations such as cardiac surgery [20]. At the end of the last century, with the advancement of neuroscience and medical research, researchers began to explore the pathogenesis of POCD. It has been found that the patient's factors, such as age, type of surgery, and underlying disease, are important risk factors for POCD. In recent years, with advances in mechanistic research, it has been found that factors such as inflammatory response and oxidative stress play an important role in the development of POCD.

Unlike delirium, there has never been a precise definition for POCD. Postoperative cognitive dysfunction (POCD) is a disorder characterized by impairments across multiple domains that are dysfunctional, can persist long after surgery and anesthesia, and for which there is no standardized method of assessment [21]. Furthermore, postoperative cognitive dysfunction is not a clinical diagnosis but a variable operational concept. After evaluation with a series of neuropsychological tests, the postoperative cognitive decline was defined by a comparison of preoperative and postoperative cognitive function [22]. Until 2018, POCD was referred to as perioperative neurocognitive disorder (PND) to include all perioperative cognitive changes. PND was categorized into five groups based on the time of onset: Preexisting cognitive changes, POD (occurring within 7 days after surgery or before discharge), delayed neurocognitive recovery (DNR, occurring from the end of surgery to 30 days after surgery), postoperative neurocognitive deficits (occurring from 30 days to 12 months after surgery), and cognitive deficits occurring after 12 months after surgery [7,16].

3. The Pathological Mechanisms of POCD

Over the past decade, researchers have conducted numerous studies on the pathogenesis of POCD. Before discussing the mechanisms of postoperative cognitive dysfunction, it is important to identify the underlying causes. The term 'underlying causes' refers to the underlying factors or conditions that contribute to the development of POCD. For example, factors such as neuronal loss or excitation-inhibition imbalance are considered to be potential causes of POCD. In the central nervous system, neurons are the basic units that perform important functions such as information transmission, processing, and storage. Loss of neurons directly disrupts the integrity and function of neural circuits, resulting in abnormal transmission and processing of neural signals, leading to cognitive and memory loss, and thus causing cognitive dysfunction [23]. In addition, neuronal loss also interferes with the synthesis, release, and metabolism of neurotransmitters. Loss of cholinergic neurons leads to a decrease in acetylcholine synthesis affecting the inter-synaptic signaling and cognitive function [24]. Excitation-inhibition imbalance is a situation in which the balance between neural excitatory and inhibitory processes in the brain is disrupted, compromising normal brain function. For example, a fine balance is maintained between the excitatory neurotransmitter (glutamate) and the inhibitory neurotransmitter (gamma-aminobutyric acid, GABA) to maintain normal brain function [25]. Excitation-inhibition imbalance affects the activity of neuronal circuits, leading to the dysfunction of neural circuits ultimately damaging the neurons [26]. Inflammatory factors produced by the inflammatory response triggered by surgical trauma can not only damage neurons, but can also affect neural signaling by modulating the neurotransmitter system and disrupting the balance between excitation and inhibition, thereby promoting the development of POCD [27,28]. Surgery and anesthesia can inhibit mitochondrial function and enhance oxidative stress, which can ultimately lead to impaired neuronal function, abnormal synaptic transmission, neurotransmitter imbalance, and even neuronal death, resulting in cognitive dysfunction [29]. In recent years oxidative stress, autophagy disorders, impaired synaptic func-

tion, and neuroinflammation are possibly involved in the development of POCD. Next, we will analyze and summarize these four mechanisms for a better understanding of the occurrence of POCD.

3.1 Oxidative Stress

In an animal experiment using a mouse model of POCD established by tibial fracture surgery, researchers observed significant oxidative stress damage in the hippocampus of POCD mice, suggesting that mitochondrial oxidative stress may contribute to postoperative cognitive dysfunction [30]. Initially, oxidative stress is promoted by phagocytosis, which produces large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in response to infectious injury [31]. ROS/RNS promotes inflammation through lipid peroxidation in the center, causing damage to membrane structure (Fig. 1). These activities also interfere with electron transfer in mitochondria and inhibit neuronal energy metabolism [31–33] (Fig. 1). In addition, oxidative stress can also impair mitochondrial function by inducing structural changes [32]. This may be due to excess ROS disrupting the redox balance within the cell [34]. Excess ROS attack the mitochondria, leading to a decrease in the mitochondrial membrane potential and the release of apoptosis-associated factors such as cytochrome C. The mitochondrial membrane potential decreases with the release of cytochrome C. Cytochrome C binds to apoptosis-activating factor-1 (Apaf-1), which activates the caspase cascade and ultimately leads to neuronal apoptosis [34,35].

Oxidative stress leads to neuronal and synaptic death, which accelerates cognitive deterioration [33]. Netto *et al*. [36] examined the expression of oxidative damage and antioxidant enzymes (superoxide dismutase-SOD and catalase-CAT) in the hippocampus by detecting ROS/RNS in POCD induced by tibial fracture surgery in rats. The results showed that rats developed cognitive decline associated with central oxidative stress and mitochondrial dysfunction. Surgical trauma damaged the antioxidant function leading to elevated ROS/RNS, and these reactive substances caused oxidative damage leading to mitochondrial respiratory dysfunction, which affected neuronal energy metabolism and led to neuronal deformation and necrosis, triggering altered cognitive function (Fig. 1).

Sirtuin3 (SIRT3) is a class III histone deacetylase (HDAC) that is highly expressed in the brain [37]. SIRT3 regulates the mitochondrial function, and it also plays a role in extending the human lifespan [38]. Anesthesia and surgery down-regulates SIRT3 in the CA1 region of the hippocampus in aging mice, promoting oxidative stress, which further leads to microglial activation and hippocampal neuroinflammation, thereby decreasing postoperative cognitive function in aged rats [39]. Oxidative stress from anesthesia and surgery causes damage to lipids and proteins [36,40], and both antioxidant endogenous defenses and mitochondrial respiratory function are disrupted [36,40,41]. It also leads to memory impairment caused by reduced brain-derived neurotrophic factor (BDNF) levels [36,41].

A study has shown that up to 60% of sepsis survivors exhibit permanent cognitive deficits [42]. Sepsis induces the production of ROS/RNS, which triggers lipid peroxidation in the cerebral vasculature and brain parenchyma [32,42]. The lipid peroxidation chain reaction further generates free radicals in the brain, which contribute to localized inflammation and promote neuronal energy depletion [43]. The oxidative metabolism of the brain is damaged, and this leads to brain dysfunction, which causes cognitive changes. Both calmodulin-dependent protein kinase II (p-CaMKII-Thr-286) and cAMP response element-binding protein (p-CREB-Ser-133) are significant mediators in regulating synaptic long-term potentiation (LTP) in the hippocampus, which is the physiological basis for memory formation [44,45]. Song *et al*. [33] found that mice anesthetized by isoflurane for six hours developed cognitive deficits within 3 days, and the expression levels of SOD, P-CaMKII, P-CREB, and BDNF in the hippocampal region were downregulated. These findings further emphasize the close link between oxidative stress and POCD.

N-methyl-D-aspartate receptors (NMDARs) are a class of glutamate receptors that play a key role in learning and memory processe [46]. NR2B is one of the subunits of NMDAR, and it has been shown that the downregulation of its phosphorylation level is relative to impaired spatial learning in rats [47]. Excessive ROS can oxidatively modify NR2B, altering its structure and function, and leading to overactivation or abnormal function of NR2B [30]. Abnormal activation of NR2B triggers intracellular calcium overload and activation of reactive oxygen species-producing enzymes, leading to a further increase in ROS, forming a vicious cycle between oxidative stress and NR2B abnormalities and exacerbating neuronal damage [48]. Isoflurane is a common inhalation anesthetic, and it has been demonstrated that it impairs the stability of the NR2B/CREB pathway through oxidative stress in mice, which leads to cognitive dysfunction [49]. In addition, aggregation of the neuronal microtubule-associated protein Tau is associated with neurodegenerative diseases [50]. It has been shown that oxidative stress possibly plays a driving role in the hyperphosphorylation and aggregation of tau proteins [51].

3.2 Autophagy Disorders

Developing the nervous system is crucial for the normal function and maintenance of the brain. Autophagy not only plays an important role in neurodevelopment in neuronal precursors but also regulates axon growth and synapse formation [52]. Ka *et al*. [53] found that autophagy was significantly activated, and progenitor cell proliferation was inhibited in the mouse brain after selective knockdown of the *MTOR* gene in animal experiments, which led to a decrease in the number of interneurons in the cerebral cortex. This suggests that autophagy has a key role in regulating

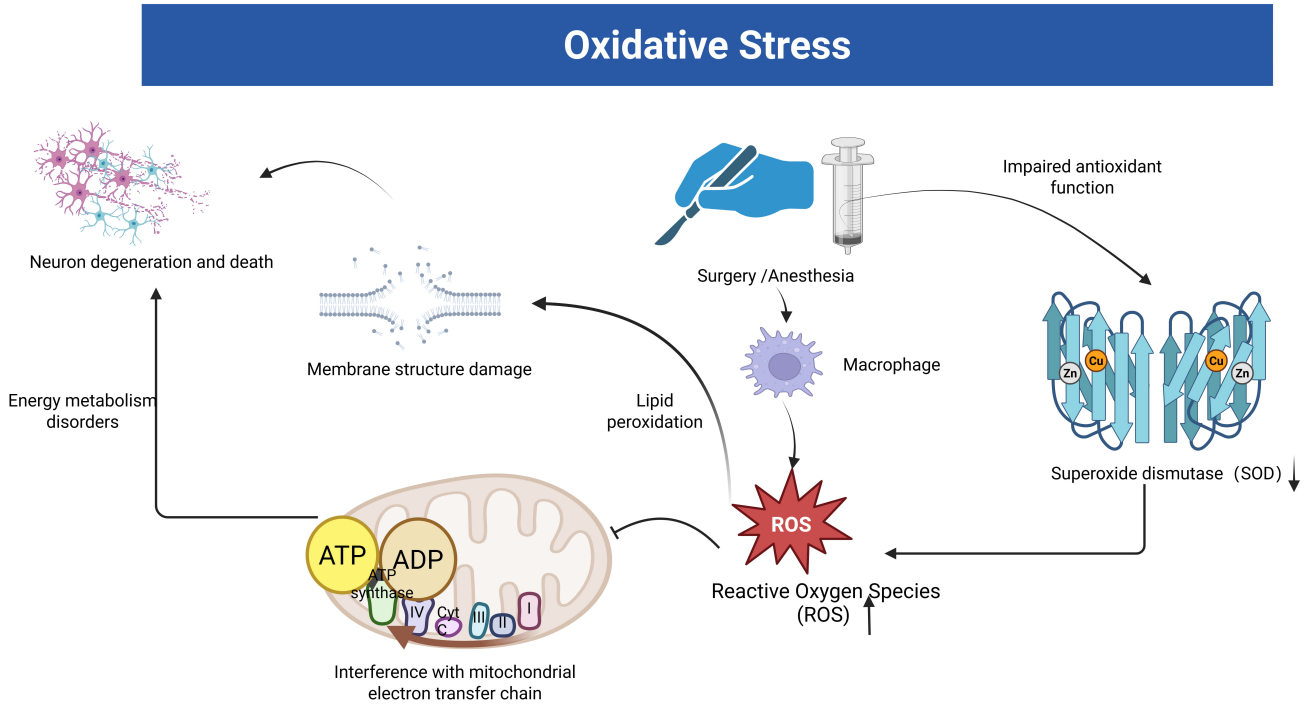

Fig. 1. The link between oxidative stress and postoperative cognitive dysfunction (POCD). The figure illustrates the oxidative stress hypothesis of POCD induced by surgery and anesthesia. Stress facilitates the production of large amounts of reactive oxygen species (ROS) by phagocytic cells. Subsequently, these ROS impair mitochondrial function, disrupt membrane structures, and hasten neuronal degradation and death. Stress also exacerbates the body's impaired antioxidant defense, resulting in reduced superoxide dismutase (SOD) activity. The figure was created with https://www.biorender.com.

neuronal development. Ribas *et al*. [54] found from animal experiments that inhibition of autophagy with an autophagy inhibitor results in axon regeneration, promoting long-term stabilization of axons and enhancing axon sprouting. In Drosophila, loss of neuronal autophagy leads to reduced synapse formation [55]. This suggests that autophagy acts as a positive regulator of development at the synaptic level. Autophagy is a central molecular pathway for maintaining cellular and organismal homeostasis and is critical for maintaining post-mitotic neuronal homeostasis [56]. In the context of neurodegenerative diseases, a study has shown that induction of autophagy is a neuroprotective response [57].

Sequestosome-1 (SQSTM1)/p62 is an autophagy receptor protein for selective autophagy that is causally associated with the development of several neurodegenerative diseases [58]. Impaired autophagy leads to toxic accumulation of damaged proteins and organelles as well as autophagy-specific substrates such as SQSTM1/p62 in mammals, which are inextricably linked to physiology and disease [59]. Defects in autophagic activity and loss of basal autophagy levels lead to neurodegeneration [60].

Autophagy is a major intracellular pathway for the degradation and recycling of long-lived proteins and organelles [61]. Damaged organelles, long-lived or abnormal proteins, and redundant or aged cytoplasmic fractions are partially eliminated by the autophagy-lysosome system, protecting cellular function and tissue homeostasis [62,63]. Autophagy disorders cause abnormal proteins such as β-amyloid (Aβ) and tau proteins to accumulate in neurons [52]. Aβ aggregates to form oligomers that activate neuroinflammatory responses, impairing synaptic function and interfering with message transmission between neurons. The aggregation of tau proteins after over phosphorylation forms neurogenic fiber tangles, which damage the cytoskeleton of neurons and ultimately lead to neuronal death and cognitive dysfunction [52]. Autophagy is categorized into microautophagy and macroautophagy as well as chaperone-mediated autophagy (CMA) based on mechanism and function [64]. For example, pathogenic variants of α-synuclein and truncated tau interfere with the normal function of the CMA (chaperone-associated autophagy) translocation complex, thereby reducing the degradation of damaged and misfolded cytoplasmic proteins, which accumulate in the cytoplasm and impair neuronal function [65,66].

Defective autophagy is thought to be associated with the development of aging and age-related neurodegeneration due to the decline in autophagic capacity and the aggregation of abnormal and dysfunctional molecules, organelles, and proteins in aging tissues [67]. Autophagy disorders lead to the accumulation of damaged mitochondria in neurons, and the energy metabolism of these damaged

mitochondria is impaired, leading to a decrease in the production of ATP and an insufficient supply of energy to neurons [52]. These damaged mitochondria also produce excessive reactive oxygen species (ROS), which trigger oxidative stress, further damaging the cells, affecting neuronal function, and contributing to cognitive impairment [29]. Inflammation in the aging brain is thought to be associated with activation of the NF-κB transcription factor system, which is a potent inhibitor of autophagy [68–71]. Activation of the NF-κB system can inhibit autophagy [72,73], which leads to neurodegeneration [68,69]. Redox-sensitive transcription factor (P53) is associated with genome stability and is involved in the regulation of the cell cycle, DNA repair, and apoptosis [61]. P53 regulates autophagy [74,75] and upregulates autophagy protein transcription through the downregulation of the IGF-1/AKT-1/mTOR pathway [61,75–77]. SIRT1 is a NAD-dependent deacetylase that plays a key role in metabolism, immunity, and aging and can affect the level of neurodegeneration through direct activation of autophagy [78–80]. Mitochondrial autophagy dysfunction was associated with sevoflurane-induced cognitive dysfunction, which may be related to the inhibition of mitochondrial respiration and mitochondrial autophagic fluxes by sevoflurane treatment, changes in mitochondrial morphology, and impaired lysosomal acidification [81].

Wang *et al.* [82] constructed an animal model of POCD and found that oxidative stress and neuroinflammation were significantly activated and autophagy in the hippocampus was reduced after abdominal surgery in aged mice. The cognitive ability of the mice was improved after pretreatment with electroacupuncture. Detection of superoxide dismutase (SOD), reactive oxygen species (ROS), number of hippocampal microglia, and autophagy markers showed oxidative damage, autophagy dysfunction, and reduced neuroinflammation. Increased oxidative stress in the hippocampus following anesthesia and surgery contributes to microglial activation, leading to neuroinflammation in turn, microglia-mediated neuroinflammation exacerbates oxidative stress in the brain [39]. Under normal conditions, defective proteins and organelles are cleared through the autophagy pathway. However, surgical intervention disrupts hippocampal autophagy, impairing cellular waste clearance and increasing oxidative damage [83]. Zhang *et al.* [84] found that dexmedetomidine promotes the degradation of NLRP3 inflammatory vesicles via the autophagy-ubiquitin pathway, which reduces the inflammatory response in the hippocampus and improves cognitive impairment in mice. Thus the role of autophagy in POD/POCD may be interconnected with neuroinflammation and oxidative stress.

3.3 Impaired Synaptic Function

A study has shown that synaptic plasticity is a key molecular mechanism for learning and memory [85]. The total number of dendritic crossings within the range of 70 to 130 μm is significantly reduced in aged rats following anesthesia and surgical induction [86,87]. An animal study demonstrated that exposure to high concentrations of sevoflurane resulted in a significant decrease in the expression level of synaptotagmin 1 (Syt1) in the rat hippocampus, which impeded the release of presynaptic neurotransmitters and reduced the efficiency of synaptic transmission [88]. In addition, total dendritic length and spines were also reduced after anesthesia and surgery, which may be related to impaired synaptic plasticity in the CA1 region of rat hippocampus after anesthesia and surgery [41].

BDNF plays an important role in the development, maintenance, and function of the vertebrate nervous system, regulating the expression of proteins (neurotransmitters and ion channels) that are essential for normal neuronal function [89]. Brain-derived neurotrophic factor (BDNF) is one of the most important neurotrophic factors in the mammalian brain and is closely associated with the control of neuronal and glial cell differentiation, neuroprotection, and the regulation of synaptic transmission and plasticity, functions that are critical for cognition and memory [90–92]. The binding of BDNF to TrkB receptors stimulates neuronal differentiation and dendritic differentiation in the hippocampal subgranular zone, and BDNF deficiency inhibits dendritic branching and disrupts synaptic plasticity [93,94]. The function of BDNF in regulating synaptic plasticity is dependent on the synergistic effect of NO [95]. However, the specific relationship between NO and the neurotrophic factors involved in its regulation is unclear. Prostaglandin E2 (PGE2) regulates hippocampal synaptic transmission and plasticity [96,97].

EP3, one of the receptor subtypes of PDE2, is highly expressed in the brain and has the highest affinity for PGE2 [98]. The PGE2- EP3 signaling pathway was shown to be involved in the development of POCD after cesarean section in aged mice [97]. CREB, BDNF, and activity-regulated cytoskeleton-associated protein (Arc) are involved in the regulation of synaptic plasticity [99,100]. EP3 induces a decrease in the intracellular levels of calcium and cAMP by inhibiting Ras/MAPK of the PKA pathway, which down-regulates the phosphorylation levels of CREB and its downstream products, Arc and BDNF, and thus inhibits altered synaptic plasticity [97]. Therefore, EP3 is expected to be a key breakthrough point for the treatment of POCD. Impaired synaptic function, which affects learning and memory functions, may be one of the mechanisms leading to POCD.

3.4 Neuroinflammation

POCD is the result of a combination of factors. Many animal studies have shown an increase in inflammatory markers in plasma and cerebrospinal fluid (CSF) even after aseptic surgery, suggesting that inflammation in the central nervous system may be one of the pathogenetic mechanisms for postoperative cognitive changes [2,101,102].

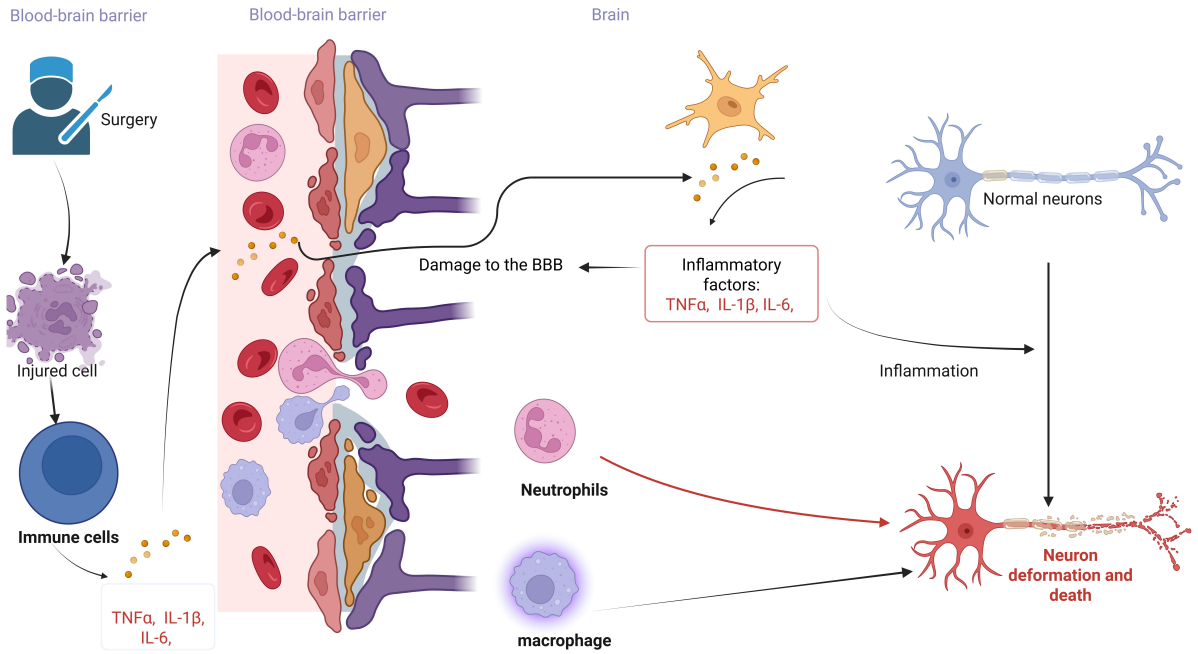

Fig. 2. The link between neuroinflammation and POCD. The figure illustrates the neuroinflammatory hypothesis of POCD induced by surgery and anesthesia. Peripheral immune activation leads to the production of numerous inflammatory factors, which compromise the integrity of the Blood-Brain Barrier (BBB). Inflammatory factors entering the brain stimulate immune cells to secrete additional inflammatory factors, thereby initiating an inflammatory response. These inflammatory factors, along with peripheral immune cells traversing the blood-brain barrier, result in the deformation and death of normal neurons. The figure was created with https://www.biorender.com.

Neuroinflammation is an inflammatory response within the brain or spinal cord [103]. Surgical trauma can lead to massive immune cell infiltration, inflammatory cytokine expression, and glial cell activation, resulting in a neurotoxic response to the central nervous system [2,104,105] (Fig. 2). Surgery induces tissue damage and inflammatory processes, triggering the release of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor (TNF-α), and prostaglandins [106] (Fig. 2).

Although the presence of the blood-brain barrier limits the entry of inflammatory factors into the CNS, peripheral inflammation can compromise the integrity of the blood-brain barrier, allowing blood cytokines to directly affect the brain and trigger neuroinflammation [107] (Fig. 2). During surgery, the inflammatory response triggered by surgery and anesthesia promotes increased expression of inflammatory factors in plasma, impairing the structure and function of the intestinal barrier [108]. Inflammatory factors can enter the circulation through the damaged intestinal barrier [109]. Osburg *et al.* [110] found that TNF-α, an inflammatory factor, can disrupt the blood-brain barrier and cross it. On the one hand, these inflammatory factors upregulate the expression of matrix metalloproteinases (MMPs), which can degrade the tight junction proteins and extracellular matrix components of the blood-brain barrier, thus destroying its integrity [111,112]. On the other hand, when the blood-brain barrier is disrupted, peripheral inflammatory cells and more inflammatory factors enter the brain and activate microglial cells. This triggers neuroinflammation, damages neurons and synapses, and leads to cognitive dysfunction [113]. Adenosine triphosphate (ATP), alarmins, and cytokines are released in large quantities from the trauma site into the brain and activate microglia [114,115]. Activated microglia may affect learning and memory by releasing pro-inflammatory cytokines [116].

Peripheral surgery induces an innate immune response, which triggers an inflammatory process in the hippocampus mediated by the cytokine interleukin-1β (IL-1β), and finally memory impairment [117]. Long-term potentiation (LTP) was previously mentioned as the basis for memory and learning, and elevated levels of IL-1β can interfere with and inhibit hippocampal LTP [117,118]. IL-1β also enhances glutamate neurotoxicity, which triggers cognitive dysfunction [118,119]. In a mouse model of surgically induced cognitive dysfunction, TNF-α promotes the release of IL-1, which contributes to neuroinflammation and cognitive decompensation in mice [120]. In addition, peripheral immune signals can also be transmitted to the brain via sensory nerves through the lower brainstem [121,122], leading to neuroinflammation. In several clinical trials, elevated levels of inflammatory markers in the cerebrospinal fluid of patients who developed cognitive dysfunction after surgery have been directly correlated with cognitive func-

tion [123–125]. An animal study demonstrated that TNF-α-induced blood-brain barrier dysfunction in mice triggered inflammation that migrated to the hippocampal region of the brain and activated NF-κB, leading to memory impairment [126]. The CNS-specific protein (S100β protein) is a neurotrophic factor (at physiological concentrations) that is involved in CNS development and responds to inflammatory responses, ischemia-reperfusion, and oxidative stress [127,128]. In some clinical studies, S100β protein levels were significantly elevated in patients who developed POCD after surgery [129,130]. This may be related to the fact that high concentrations of S100β protein stimulate the expression of pro-inflammatory cytokines, induce apoptosis, exert neurotoxic effects, and promote neuroinflammation, which ultimately leads to neurodegenerative diseases [131–133].

4. The Animal Models of POCD

The construction of animal models is indispensable for studying the pathogenesis of POCD and exploring therapeutic approaches. The current construction of animal models of POCD is based on different mechanisms of surgical and anesthetic induced POCD. The following summarizes the construction of POCD animal models (Table 1, Ref. [134–139]). The construction of animal models by surgery is based on the induction of POCD by the inflammatory response caused by surgical trauma [140–142]. In recent years, the inflammatory response has been recognized as the key factor in the development of POCD. The surgical construction of an animal model of POCD enables the analysis of the relationship between factors such as the extent and duration of surgical trauma and the occurrence of POCD. It also allows for the comparison of differences in POCD induced by general anesthesia. Surgeries known to induce POCD in mice include orthopedic procedures [140], partial hepatectomy [141], carotid artery exposure [142], and other surgical interventions. Among them, the tibial fracture mouse model is the most common POCD model, which may be related to the high incidence of POCD in orthopedic-related surgeries [1]. Although different types of surgery can induce POCD in animals, the extent and specific aspects of cognitive function are different. Anesthesia treatment allows the establishment of an animal model of POCD, which is induced by anesthetic drugs mainly by acting on N-methyl- D-aspartate (NMDA) and γ-aminobutyric acid (GABA)-mediated pathways. These two pathways play a key role in normal neurodevelopment [143]. Inducing POCD in animals using anesthetic drugs enables the analysis of the impact of drug concentration and duration of exposure on POCD. The combination of surgery and anesthesia for constructing a POCD model can more comprehensively simulate the occurrence of clinical POCD, analyze the effects of different combination methods, and is suitable for mechanism research.

How to determine the occurrence of POCD in experimental animals is mainly measured by analyzing animal behavioral science. Behavioral experiments are important experimental methods in animal research. Morris water maze experiment (MWN) can be used to test spatial learning, memory, and cognitive flexibility in mice by observing the path trajectory, latency, and the number of times the animal traverses the platform [144]. Elevated plus maze (EPM) and open field test (OFT) can be used to measure anxiety-like behavior in mice [145]. Fear Conditioning Tests (FCTs) are primarily used to assess learning and memory in animals by observing the percentage of time spent in freezing position, latency of fear response and other indicators [146]. Barnes maze can be used to test spatial navigation and long-term memory skills by recording the latency of the animal to find a target hiding place, the number of errors, path efficiency and other metrics [147]. New Object Recognition Test (NORT) can be used to assess the learning and memory abilities of animals by recording the time they spend searching for familiar and new objects [148]. Pathological biopsy of the brain tissue of the experimental subjects and analysis of various biomarkers in the circulatory system are more reliable methods to verify the success of animal model establishment.

Differences between animals and humans in clinical manifestations and pathophysiologic processes may affect the translation of results from animal models to clinical applications. Individual differences among animals, differences in experimental environments, and differences in experimental techniques all affect model stability and reproducibility. Although animal models play a crucial role in POCD research, studies have been limited to rats and mice with no studies reported in nonhuman primates [149–151].

5. Clinical Trials of POCD

Clinically, postoperative cognitive dysfunction occurs in elderly patients undergoing surgical procedures requiring anesthesia, especially in orthopedic surgeries. POCD is diagnosed in the clinic and relies on cognitive functioning test scales. The Mental State Examination (MMSE) is the most widely used cognitive screening tool. It is less time-consuming and easier to administer but has limitations. The MMSE is less sensitive to detecting mild cognitive impairment and dementia. Additionally, results may be influenced by a person's literacy level, potentially leading to misclassification [152]. The Montreal Cognitive Assessment Scale (MoCA) is more specific for characterizing lesions in patients with mild cognitive impairments but is susceptible to cultural and educational influences [153]. The Wechsler Intelligence Scale is a widely used tool for assessing intelligence, which includes various aspects such as verbal skills and can reflect a person's cognitive ability more comprehensively but the test items are time-consuming and affected by the level of education [154]. Denbrooke's Cogni-

Table 1. Summary of the construction of the POCD animal models.

Laboratory animals	Intervention methods	Tests	Biomarkers	Behavioural disorders	Advantages	Disadvantages
13–18 month-old male rats [134]	Exposure to 3% sevoflurane	MWM, EPM, OFT	Number of microglia in the CA1 region of the hippocampus, expression of TNF-α, IL-1β and IL-6	Decreases in time and number of entries into the platform quadrant versus the central region and anxiety behaviors	Fast induction and awakening of anesthesia, suitable for prolonged anesthesia, low respiratory tract irritation	High equipment requirements (special evaporation tanks required), high cost
20-month-old male rats [135]	Exposure to 3% Isoflurane	MWM	Expression of expression of Hypoxia-inducible factor-1α (HIF-1α) protein	Prolonged escape latency and prolonged latency to enter the target area	Easy to adjust the depth of anesthesia, good stability, low cost	Cardiovascular system depression (hypotension, decreased heart rate)
20-month-old male rats [136]	Tail vein injection of Propofol (30 mg/kg)	MWM	Expression of GSK-3β, Total and Phosphorylated Tau, Cell Cycle Protein D1, P27kip-1 in the hippocampus	Prolonged latency and shortened target quadrant retention time	Easy to operate and highly reproducible	Poor controllability
18-month-old mice [137]	Partial hepatectomy	MWM	Expression of IL-1β and IL-6 and Microglia Activity, expression of Tight Junction Proteins, NLRP3 Inflammatory Vesicles and Downstream Proteins, and NF-κB Pathway Proteins	the residence time stayed in the target quadrant and number of the platform crossing time was significantly reduced	Highly controllable (adjustable excision ratio)	High mortality rate and high operational requirements
16-month-old mice [138]	Fracture of the tibia under isoflurane anesthesia (3% isoflurane for induction and 1.5% isoflurane for maintenance)	OFT, FCTs	Expression levels of BDNF, proBDNF, TrkB, p-TrkB, p75NTR, and Synapse Proteins	Hippocampus-dependent memory loss	Simulation of clinical fracture pathology allows study of postoperative cognitive and inflammatory responses in conjunction with anesthesia	Difficult surgery and complex postoperative pain manage
8-week-old male mice [139]	Right carotid artery exposure under 1.8–2% isoflurane anesthesia	Barnes Maze and Fcts	Expression levels of Neuroligin 1	Increased time required to identify target boxes	Motor function unaffected, exploring the link between changes in vascular function or hemodynamics and cognition	Possible nerve and tissue damage, technically demanding

Summarize the current construction of POCD animal models from the selection of experimental animals, intervention methods, experimental projects, biomarkers, etc. MWM, Morris water maze; EPM, elevated plus maze; OFT, open field test; GSK-3β, glycogen synthase kinase 3 beta; NLRP3, nod-like receptor family pyrin domain-containing 3; FCTs, fear conditioning tests; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; p75NTR, p75 neurotrophin receptor.

Table 2. Summary of clinical trials for POCD.

Age	Name of surgery	Anesthesia method	Cognitive measures	Biomarkers
60–90 years [158]	Cardiac surgery	Intravenous-inhalation combined anesthesia	The Confusion Assessment Method (CAM) and the Montreal Cognitive Assessment (MoCA)	/
≥65 years [159]	Unilateral total hip replacement or total knee replacement	Combined spinal-epidural anesthesia (CSEA) with sedatives	The neuropsychological test battery: MoCA, Stroop color-word test (SCWT), Digit span test, Digit symbol test, Associative learning and memory test	/
>45 years [160]	Non-cardiac surgery	Intravenous general anesthesia	The mini-mental state examination (MMSE), the neuropsychological test battery: Chinese auditory learning test (CALT), the digit span test (DST), the judgment of line orientation test (JLOT), and language fluency test (VFT)	the plasma microRNA-221-3p level
≥65 years [161]	Hip fracture surgery	general or subarachnoid (spinal) anesthesia	CAM, MMSE	/
≥60 years [162]	radical surgery for gastrointestinal tumor	Intravenous-inhalation combined anesthesia	MMSE	S100calcium-binding protein beta (S100β) and C-reactive protein (CRP), Interleukin-6 (IL-6)
≥45 years [163]	Thoracic surgery	Intravenous-inhalation combined anesthesia	The neuropsychological test battery	/

Summarize current research on POCD clinical trials from different perspectives, including patient age, anesthesia method, surgical approach, cognitive assessment methods, and blood markers. The Confusion Assessment Method (CAM) and the Montreal Cognitive Assessment (MoCA).

tive Examination III is a comprehensive cognitive functioning assessment tool that evaluates impairments in a variety of cognitive domains, including attention, memory, language, etc [155]. It is superior to other screening tests for mild cognitive impairment, but the reliability of the results depends on the number of items tested and is not a complete substitute for more specialized neuropsychological tests [156].

In addition, in recent years, it has been widely recognized that neuroinflammation is associated with postoperative cognitive dysfunction, and the inflammatory factors listed above, such as IL, C-reactive protein (CRP), TNF-alpha, and S100β proteins, and neuron-specific enolase (NSE), are being used as diagnostic markers of POCD. Because the inflammatory response fades after surgery, this is not favorable for predicting the development of late POCD. In recent years non-coding RNAs (ncRNAs) have been shown to potentially play an important role in POCD and are closely associated with neuroinflammation, Aβ accumulation/tau hyperphosphorylation, neuronal apoptosis, and oxidative stress [157]. ncRNA is expected to be a biomarker for the diagnosis and treatment of POCD. However, there are not many studies on ncRNA in the clinic. Below we summarize several sets of clinical studies on POCD (Table 2, Ref. [158–163]).

6. The Gap between Clinical Research and Basic Trials

At present, regarding the construction of animal models of POCD, most of them choose rodents as experimental subjects. The construction of animal models relies on surgical and anesthesia treatments, and most existing studies have focused on anesthesia treatments alone [134–139], with some opting for a combination of surgery and anesthesia. However, the independent contribution of surgery and anesthesia to postoperative cognitive function is not clear. It has been suggested that it is surgical trauma, not anesthesia, that causes POCD [164]. Whether anesthesia alone leads to postoperative cognitive dysfunction is controversial [10].

In clinical trials, anesthesia and surgery are often combined, so models for future animal studies should be better designed to reflect clinical settings. The definitive clinical diagnosis of POCD relies on neurocognitive test scales, while basic research determines the occurrence of POCD in experimental animals through behavioral tests. However, the cognitive evaluation scales for animals and humans are not completely standardized and may be influenced by subjective factors of the researchers. In clinical studies, it is the systematic assessment of the patient that determines POCD, which is an individual-based assessment process [158–163]. The assessment of cognitive function in surgical patients covers the entire perioperative period. In contrast, in current animal studies, experimental animals are often evaluated only once after anesthesia and surgery, which is detrimental to the detection of POCD in experimental animals [134–139]. Additionally, differences in assessment methods between basic and clinical research can hinder POCD detection. Significant variability in the type, number, and timing of tests further complicates the understanding of POCD. Although most of the clinical and basic studies rely on detecting inflammatory factors in the blood to predict POCD, its specificity remains low [165,166].

In addition to this, blood, cerebrospinal fluid, hippocampus, and other tissues from animals can be studied. While brain tissue is difficult to obtain, inflammation-related biomarkers are mostly analyzed based on patient blood specimens. In the future, if there are neuroinflammation-specific markers capable of labeling in vivo brain tissue, it will have a profound impact on the development of POCD research. Therefore, we need more clinically relevant animal experiments to provide more valuable evidence for the pathogenesis of POCD. Through animal experiments, we can provide strong support for clinical research and faster solutions for the prevention and treatment of POCD, so that POCD patients can be better managed.

7. Conclusions

Although the major risk factors for POCD are recognized, there is no clinical or standardized method for identifying high-risk patients. Patients who developed postoperative cognitive dysfunction had no significant changes in imaging and relatively atypical clinical presentations. Therefore, extensive perioperative screening is necessary and desirable to identify individuals at risk for POCD. Currently, there is no treatment for POCD and no standardized means of routine assessment. There is a clear need for a treatment or medication that can prevent or treat POCD, especially in high-risk populations. Cognitive function involves complex mechanisms and factors, and it is difficult to improve patients' cognitive function with medication alone.

The underlying pathogenesis of POCD is unclear due to conflicting results from different studies and controversial evidence. In addition, effective postoperative follow-up is lacking, and the incidence of POCD in China is unknown. Although many drugs have been proposed to improve POCD in animal studies [108,167], they have always been limited in clinical application. Future research should also focus more on finding risk factors outside of surgery that would be more beneficial to patients at risk for postoperative cognitive impairment. Although many mechanisms may contribute to postoperative cognitive dysfunction, including apoptosis, neuroinflammation, oxidative stress, and autophagy, are involved in cognitive dysfunction induced by anesthetic drugs or surgery, the exact molecular mechanisms are unknown. Further studies on the mechanism, prevention, and treatment of POCD are needed in the future.

Author Contributions

YL and QP did the literature search, prepared the figures, and drafted the paper. JL and LH assisted in collecting and organizing reference texts and provided advice on designing and plotting diagrams. HZ presented the paper conceptualization and design, writing, outline, and final approval of the published version of the article. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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