Postoperative Cognitive Dysfunction and the Protective Effects of Enriched Environment: A Systematic Review

Momin Hua^a Jia Min^b^aFirst Clinical Medical College, Nanchang University, Nanchang, PR China; ^bDepartment of Anesthesiology, First Affiliated Hospital of Nanchang University, Nanchang, PR China

Keywords

Postoperative cognitive dysfunction · Enriched environment · Neuroinflammation · Alzheimer's disease

Abstract

Background: Currently, the number of individuals who undergo surgery is greatly increased. As a consequence, postoperative cognitive dysfunction (POCD) has gradually gained more attention. **Summary:** POCD is a perioperative complication requiring sensitive preoperative and postoperative neuropsychiatric tests, and its incidence in both cardiac and noncardiac surgery is high, especially in elderly individuals. Surgical, patient, and anesthetic factors may all lead to the occurrence and development of POCD. The key mechanism of POCD may be the inflammatory response of the central nervous system during surgery, which is similar to that of Alzheimer's disease (AD). Enriched environment (EE), a factor that can significantly improve and prevent neurodegenerative diseases, may have a beneficial effect on POCD. **Key Messages:** This review aims to elucidate the mechanism of the occurrence and development of POCD, analyze the possible influence of EE on POCD at the molecular level, and provide a direction for its treatment.

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Introduction

Postoperative neurological complications pose a great threat to human health, especially in elderly patients. Postoperative cognitive dysfunction (POCD) is a syndrome defined by the continuous decline of cognitive performance, including attention, executive function, memory, visual spatial ability, and psychomotor speed, in a series of neuropsychological tests before and after surgery [1]. Globally, it is estimated that 50% of all older individuals have undergone at least one operation and it is known that changes associated with aging affect an individual's ability to withstand injury, surgery, and anesthetic stress [2]. Thus, POCD has far-reaching social and economic impacts, as cognitive decline is associated with loss of independence, lower quality of life, and death [3]. Age, education level, preoperative cognitive ability, and complications are all considered to be factors affecting the occurrence and development of POCD [2]. Meanwhile, studies have suggested that some preoperative factors may trigger the neuropathogenesis of Alzheimer's disease (AD) to cause POCD [4]. Enriched environment (EE), which improves behavioral, cellular, and molecular defects in animal models, can provide animals with the optimum conditions to enhance exploration, cognitive activities, social interaction, and physical exercise [5]. This suggests that EE may become a strategy for the prevention and treatment of POCD.

Definition and Incidence of POCD

The earliest description of POCD was put forward by Bedford [6] in 1955. According to the International Society of Postoperative Cognitive Dysfunction (ISPOCD), POCD is a defect in ≥ 1 areas of the mental state observed in patients after operation [7]. It is a subtle thought process disorder that can affect different cognitive areas such as verbal memory, language comprehension, visual memory, visual spatial abstraction, attention, and executive function. POCD is defined as a syndrome characterized by a continuous decline in cognitive performance in a series of neuropsychological tests before and after surgery [1].

There are no formal criteria for the evaluation and diagnosis of POCD, which require sensitive preoperative and postoperative neuropsychiatric tests. Therefore, the current incidence of POCD varies greatly according to the statistical definition of the cognitive data applied. Consequently, it is necessary to develop consistent diagnostic criteria for POCD to conduct a more meaningful study of this cognitive dysfunction [3].

Early studies showed that POCD occurs more frequently after cardiac surgery than other types of surgery [8], with the highest incidence of 30–70% at discharge, followed by 20–30% 6 months after the operation and 15–25% 12 months after the operation [9]. In 1998, a multinational research team published the first large-scale prospective study to describe cognitive decline after noncardiac surgery [7]. Moller et al. [7] studied the risk factors for POCD in 1,218 patients >65 years of age who underwent noncardiac surgery, and then compared them with 321 controls who did not undergo surgery but also underwent repeated neuropsychological tests. The study showed that the prevalence of POCD was 26% 1 week after the operation and dropped to 10% at 3 months after the operation, and a similar prevalence was found 12 months postoperatively. In the nonoperative controls, a 3% incidence of POCD was found for each time period. Monk et al. [10] also recorded the presence of POCD in patients discharged from noncardiac surgery. Their research suggested that 36.6% of surgical patients who developed POCD were 39 years old, 30.4% were aged between 40 and 59 years, and 41.4% were ≥ 60 years. Three months later, 12.7% of the patients >60 years still had POCD. However, recent randomized studies found that the incidence of POCD is similar in cardiac surgeries regardless of whether cardiopulmonary bypass (CPB) is performed [11], which is worthy of further study.

Factors Affecting the Occurrence and Development of POCD

The main risk factors for POCD include major invasive surgery, the duration of anesthesia, an advanced age, a history of alcoholism, the use of anticholinergic drugs, and other perioperative events. The release of cytokines caused by the systemic stress response induced by anesthesia and surgery may lead to changes in brain function and participate in the development of POCD [12].

Patient Factors

Advanced age is the highest known risk factor associated with POCD. The ISPOCD1 study analyzed the risk factors for POCD in patients undergoing noncardiac surgery; it found that, 3 months after the operation, the incidence of POCD was 7% in patients aged 69 years and 14% in patients >69 years of age [7]. Advanced age is characterized by impaired functions in many regulatory processes, which can lead to increased physical and mental fragility as well as a reduced ability to deal with physical stressors such as anesthesia and surgery. In addition, older individuals are more likely to have a variety of underlying diseases like diabetes, renal insufficiency, or cardiovascular disease [12]. Additionally, elderly patients tend to have more risk factors for neurovascular diseases, more white-matter damage, and lower cognitive reserves [13], all of which increase the risk of perioperative complications.

Some studies have suggested that POCD incidence is lower in patients with a higher level of education than in patients with a lower level of education. In people with a higher level of education, the brain is constantly exposed to challenging psychological activities that may slow the development of dementia by utilizing the cognitive reserves and improving the efficacy of synapses, thus changing the progression of neuronal damage [2]. The duration of a person's educational and vocational activities may increase cognitive reserves, making some people less vulnerable to cognitive changes [14]. Moderate physical activity and social participation also play a positive role in promoting the cognitive function of elderly individuals, and elderly surgical patients who are inactive, depressed, and socially isolated are more likely to suffer cognitive impairment [2].

Perioperative Factors

The functioning of the central nervous system (CNS) depends on an adequate supply of oxygen and nutrients, effective removal of waste, and the existence of an appro-

Fig. 1. This picture depicts the CNS immune response caused by peripheral inflammation.

priate neurochemical environment. A metabolic imbalance in the brain from any cause may lead to overall dysfunction, which can lead to a decline in cognitive function after surgery [1]. Wollman and Orkin [15] reported that extreme hypocapnia during anesthesia is associated with prolonged cognitive impairment for at least 6 days after hyperventilation [1]. Obviously, to avoid postoperative cognitive dysfunction, it is essential to provide adequate oxygen to the brain and all the important organs.

Cardiac surgery and certain orthopedic surgeries can lead to a relatively high incidence of POCD. One hypothesis is that cerebral microemboli can lead to the mild neurological impairment associated with POCD [1]. The high incidence of POCD in cardiac patients is attributed to microembolic events that can cause focal cerebral infarction during CPB [12]. CPB can also cause specific activation of the inflammatory response through the immune system, ischemia-reperfusion injury, complement activation, and heparin and protamine neutralization after blood contact with artificial materials during a bypass [16]. In a mouse model, hippocampal-dependent memory impairment induced by orthopedic surgery and anesthesia was found to be associated with an increase in plasma cytokines and the activation of the interleukin (IL)-1 β pathway in the hippocampus [17]. Further studies have demonstrated that isoflurane alone activates the IL-1 β

pathway and leads to hippocampal cell damage, which may lead to related cognitive impairment [18].

Three main factors lead to cognitive impairment after cardiac surgery: embolism, low perfusion, and inflammation. The results of the experiments conducted by Ito et al. [19] show that patients with asymptomatic cerebral ischemia are more likely to develop POCD after cardiac bypass surgery. Studies have shown that there is a relationship between low preoperative levels of the anti-endotoxin core antibody and POCD in patients undergoing cardiac surgery. This suggests that a decreased immune response to endotoxin may be the cause of POCD [2]. Severe systemic inflammation can lead to multiple organ failure, including in the brain, and a variety of clinical consequences such as delirium and septic encephalopathy and ranging from mild cognitive impairment to coma [1].

Pathogenesis of POCD

Neuroinflammation Mechanism

The mechanism of POCD has not been fully elucidated, but the most accepted mechanism is neuroinflammation, especially in the hippocampus. Although cognitive processes involve multiple brain regions, the hippocampus, which contains the largest number of cytokine receptors, plays a clear role in learning and mem-

ory formation. In particular, the hippocampus contains the highest density of IL-1 receptors. Although physiological levels of IL-1 are essential for optimizing memory and learning processes, high levels are associated with decreased cognitive function in animal models. Additionally, the hippocampus appears to be particularly vulnerable to the harmful effects of elevated levels of inflammatory mediators, such as high-mobility group protein 1 (HMGB1), because of the high density of tumor necrosis factor (TNF)- α receptors and many other receptors on the surface of endothelial cells in this region [20].

Through animal experiments, Terrando et al. [21] showed that the surgical immune response plays an important role in POCD. Their studies showed that inflammatory TNF or NF- κ B signaling cascades were activated during peripheral surgery in mice, resulting in the release of cytokines and the destruction of the integrity of the blood-brain barrier (BBB). Consequently, macrophages are more likely to migrate to the hippocampus, and neutrophils are more likely to adhere to capillary endothelial cells, resulting in memory impairment. On the other hand, activating the anti-inflammatory cholinergic signaling cascade to prevent the secretion of proinflammatory cytokines can prevent damage to cognitive function. Moreover, some researchers believe that sedation and anesthesia can lead to limited ischemia of brain endothelial cells and induce hypoxia. Acute hypoxia can induce activated neutrophils to migrate and adhere to endothelial cells, which leads to the development of microthrombi and the release of powerful pressor substances, resulting in complete capillary blockage and blood flow obstruction. Therefore, the response of the CNS to systemic inflammatory mediators can lead to delayed recovery or long-term postoperative CNS dysfunction [1] (Fig. 1).

In different preclinical models of non-CNS surgery, neuroinflammation is often associated with behavioral and memory dysfunction. Previous studies have shown that chemokines and injury-related molecules (e.g., HMGB1) can activate bone marrow-derived macrophages and contribute to overall brain pathology after aseptic trauma [13]. Increased levels of the proinflammatory cytokine IL-1 β in the CNS lead to an increase in reactive oxygen species (e.g., nNOS and iNOS) which is coupled with the destruction of long-term potentiation (LTP) [20]. Studies have indicated that nNOS and iNOS increase the production of peroxynitrite, inhibit mitochondrial respiratory enzymes, and damage DNA [22] (Fig. 1).

Activation of Microglia and Astrocytes

Inflammation of the CNS also depends on the activation of microglia to drive the production of local oxidation products. Microglia express specific receptors for inflammatory signals, such as bacterial endotoxins or endogenous ligand receptors, including the HMGB1 receptor and especially Toll-like receptor (TLR)-4. The increase in peripheral inflammatory factors induced by surgery leads to morphological changes and the upregulation of TLR-4 in microglia [23] (Fig. 1). Surgical stress increases the levels of NADPH oxidases (NOX enzymes) in the brain, and NOX enzymes are key to the regulation of oxidative stress which is related to behavioral changes in mice [24]. NOX enzymes are also involved in the increased oxidative stress observed in a variety of brain diseases ranging from mental illness to neurodegenerative diseases [25].

Astrocytic S100 calcium-binding protein β (S100 β) is highly abundant in the brain and plays a crucial role in multiple homeostasis- and injury-related processes through autocrine and paracrine signal transduction. S100 β can directly induce neuronal injury or activate microglia and astrocytes and induce microglial oxide production [20]. S100 β -induced neuroinflammation mediates RAGE (advanced glycosylation end product-specific receptor) signaling in microglia. The RAGE signaling pathway may upregulate proinflammatory cytokines through the NF- κ B signaling pathway, indicating that S100 β -induced neuroinflammation may play a role in the pathogenesis of surgery-induced cognitive impairment [26] (Fig. 1).

Pathological Changes Similar to AD

Studies have suggested that POCD and AD have similar pathological changes and serological markers. Histologically, AD is characterized by neurofibrillary tangles, which consist of pairs of spiral filamentous hyperphosphorylated Tau proteins, and extracellular amyloid β plaques. The pathological effects of these changes are increased neuronal death and synaptic loss, mainly in the cholinergic neurons in the basal forebrain. The central cholinergic system plays a critical role in the formation and regulation of consciousness, learning, and memory [27]. Moreover, IL-18 is colocalized with the Tau protein and amyloid β plaques, and it mediates the hyperphosphorylation of Tau. IL-18 can affect the integrity of neurons and increase neuroinflammation in the brain, resulting in a decline in cognitive function [26].

Eckenhoff et al. [28] demonstrated that clinical concentrations of halothane and isoflurane enhanced the

oligomerization and aggregation of amyloid peptides in cell culture. Studies have also indicated that isoflurane activates an enzyme called cysteinase, which may contribute to the formation of neurofibrillary tangles and the production of amyloid β protein [29]. The amyloid β 1–42 oligomer can interfere with insulin signaling, thus impairing cognitive and metabolic processes in the hippocampus [26].

Other Molecular Mechanisms

The existence of the apolipoprotein E (ApoE) allele is also considered to be a risk factor for the development of POCD. ApoE is not only an important lipid and cholesterol transport molecule but also an immunomodulator that is constitutively expressed in the brain and upregulated after brain injury, and it exists in neurons, oligodendrocytes, microglia and astrocytes [30] (Fig. 1). ApoE has both pro- and anti-inflammatory effects, which may be related to regulating the degree of astrocyte and microglia activation [20]. In addition, IL-1 β has been revealed to stimulate the secretion of ApoE in mixed glial cultures [31].

Glutamate signaling is particularly important in long-term potentiation and supports the formation of memory. Experimentally induced peripheral inflammation fundamentally changes the activity of hippocampal neurons, LTP, and synaptic plasticity in rats. Decreased expression of the glutamate receptor subtype GluR2 leads to the enhancement of signal transduction mediated by AMPA and NMDA. Additionally, HMGB1 can enhance glutamate signal transduction through NMDA receptors and aggravate the glutamate-induced toxicity associated with the degradation process [20].

An animal study also suggested that postoperative memory impairment may be due to the anesthesia-induced upregulation of GABA-A receptors containing α 5 subunits (which can inhibit LTP) in the hippocampus. Therefore, it can be predicted that the upregulation of these receptors will result in learning and memory disorders which may induce human POCD [32].

The Definition of EE

The experimental model of Enriched Environment (EE) was first described by Donald Hebb [33] in the context of neuroscience. He compared rats allowed to roam freely in his home with rats housed in laboratory cages [34]. In subsequent experiments, there was a variety of variables including species, sex, and age, and also EE variables that contributed to the diversity of the results [35].

In the early 1960s, Will et al. [36] conducted a series of experiments to explore the effects of EE on brain development and cognitive ability; they provided a standardized model of EE conditions that is still in use today.

The classic EE definition is a complex combination of inanimate and social stimuli; in an experimental model, this is accomplished by raising a large number of animals in large groups in an environment that maintains a wide range of stimuli, including frequently changed objects (such as toys, nesting materials, and stairs). A basic component of typical EE is the opportunity to obtain a high level of voluntary physical activity on a running wheel [5]. In some experimental models, EE may also include increasing social stimulation by the addition of more animals to each cage [34]. These configurations provide richness in 3 key areas: novelty, socialization, and exercise [37].

Living in EE conditions provides animals with the optimal conditions to enhance exploration, cognitive activities, social interaction, and physical exercise [38]. This practice is thought to lead to greater physical and psychological or emotional well-being, similar to in the natural environment, and is also thought to change the physiological responses of animals and induce neurobiological changes [39].

It has been demonstrated that EE improves behavioral, cellular, and molecular defects in animal models of neurological and mental disorders, including AD, Parkinson's disease, stroke, epilepsy, Huntington's disease (HD), and schizophrenia [38]. For example, EE elevated diminished cell proliferation and neurogenesis to wild-type levels in TgCRND8 mice with AD-like pathology and upregulated the expression of plasticity-associated structural proteins in TgCRND8 mice [40]. Furthermore, in mouse models of HD, it has been demonstrated that EE delays the onset and progression of motor symptoms and cognitive deficits [41]. EE can also be used in experimental models of the daily cognitive and physical activities of humans; the application of such models may expand our knowledge of experience- and training-induced plasticity [42] as well as our understanding of the mechanisms of cognitive enrichment, thereby promoting the development of noninvasive preventive interventions for age-related neurodegenerative and other diseases [43].

The Effect of EE on the Brain

In terms of anatomical structure, EE can significantly increase the thickness and weight of the cortex, the size of the cell body and nucleus, the number of dendritic

branches, the length of dendritic spines, and the size and number of synapses [5]. It has also been suggested that EE increases the total number of granulos cells, alters dendritic complexity and spine density, and promotes vascularization in the hippocampus [44]. It also increases the expression of synaptophysin and postsynaptic density-95 protein, which leads to increased synaptogenesis. A study has shown that EE decreases neuronal density but increases the synapse-to-neuron ratio, synaptic disc diameter, and subsynaptic plate perforation [45]. Similar morphological changes are observed in the dentate granule neurons and pyramidal cells in the CA1 and CA3 regions of the hippocampus [46].

In addition, exposure to EE enhances synaptic transmission and plasticity, increases the survival of regenerated neurons, reduces apoptosis, and promotes the expression of molecules involved in neuronal signal transduction [47]. Plasticity refers to the ability of a system to change its constituent elements and internal connection network to achieve new functions under long-term environmental constraints [36]. Neuroplasticity is an inherent characteristic of the mammalian brain that enables it to adapt to environmental changes [48]. In a recent animal study, Harati et al. [49] showed that prolonged EE can prevent cognitive decline caused by aging in female rats.

Studies have confirmed that changes in brain structure and behavior after experiencing EE are related to changes in brain neurochemistry and physiology. Several aspects of hippocampal function are reported to be enhanced by EE, such as LTP, neurogenesis, dendritic spine growth, neurotrophin mRNA expression, and the activation of mitogen-activated protein kinase (MAPK) and cAMP response element-binding protein (CREB) [47]. EE also increases the ability of hippocampal neurogenesis cells to integrate into functional circuits [45], which is thought to be mediated by the recruitment of vascular endothelial growth factor (VEGF) and T cells and the activation of microglia [50].

A large number of genes respond to EE and change their expression levels; most of them belong to functional categories related to regulating neuronal structure, synaptic transmission and plasticity, neuronal excitability, and neuroprotection [5]. EE can mediate the increased survival of newly formed neurons in the hippocampus by activating transcription factors and inducing the expression of growth factors, thereby increasing resistance to brain injury. In previous studies, it has been repeatedly demonstrated that EE enhances the expression of mRNA encoding trophic factors such as NGF, BDNF, NT-3, and

GDNF as well as the number of NGF proteins and the density of NGF receptors [36].

Rosenzweig et al. [51] found, for the first time, that EE can increase the activity of acetylcholinesterase (AChE), indicating that it has an effect on the cholinergic system. Subsequent studies confirmed and extended this preliminary observation to other neurotransmitter systems that have diffuse projections to the entire brain, such as the serotonergic and norepinephrine systems [5].

The Influence of EE on POCD

EE can greatly improve the symptoms of POCD. In various learning tasks, EE has been proven to enhance memory. The EE-exposed mice performed better on the water maze task, a spatial memory test, than the control group in standard housing. Similarly, the voluntary wheel-running and treadmill training of EE have been shown to enhance spatial learning [45]. Compared with rats kept in standard living conditions, rats kept in EE conditions showed a higher level of neuroplasticity. In the EE group, the expression of nerve growth factor in the hippocampus was increased and was positively correlated with the survival and recognition ability of precursor cells in the dentate gyrus [46].

Effects of EE on Neuroinflammation and Glial Cells

The expression of the chemokines CCL2, CCL3, and CXCL2, the TNF family, and the proinflammatory cytokine IL-1 β is significantly decreased in EE rats [52]. IL-6 is mainly present in activated glial cells, and Griñan-Ferré et al. [53] proved that the expression of the IL-6 gene decreased significantly under EE conditions. EE also limited the corticosterone-induced increase in IL-6 and TNF- α mRNAs in the hippocampus and hypothalamus and the increase in IL-1 β mRNA levels in the hippocampus [54].

The results of in vitro experiments found that, after peripheral immune stimulation with lipopolysaccharide, the release of proinflammatory cytokines from microglia isolated from the aged hippocampus was higher than that from the young hippocampus. However, EE can reduce this exaggerated cytokine response, and these findings suggest that EE can prevent the development of POCD by reversing the proinflammatory phenotype of age-related microglia in the hippocampus [55]. This may be related to an increase in adiponectin (APN) in the brain induced by EE [54]. APN induces the expression of the anti-inflammatory cytokine IL-10 in human monocytes and macro-

phages [56] and inhibits the release of IL-6 from macrophages [57]. Experiments by Chabry et al. [54] demonstrated that EE reduced the percentage of microglia expressing MHC-II and its surface TLR4/CD14 complex.

In the rodent brain, an increased number of glial cells and morphological changes in these cells have been described after EE. These morphological changes may be involved in mediating the interaction between new dendritic spines and astrocyte branches [55]. Spatial learning in a water maze contributes to the induction of basic fibroblast growth factor 2 (FGF-2), which plays a key trophic role in various types of neurons and promotes the proliferation or responsiveness of astrocytes [58]. EE can also closely regulate the concentrations of ApoE and S100 β in the peri-infarct region to the levels that are most conducive to glial scar formation, synaptic plasticity, and cell growth [59].

Effects of EE on Ischemia and Oxidative Stress

Briones et al. [60] found that, during rehabilitation after middle cerebral artery (MCA) occlusion (compared with the other groups), ischemic animals receiving EE rehabilitation exhibited a significantly increased degree of dendritization in the undamaged contralateral cortex. Experiments by Ruscher et al. [61] indicated that living in EE conditions could significantly reduce the increase in ApoE and IL-1 β expression that occurs during the recovery after experimental middle cerebral artery occlusion (MCAO), and could specifically reduce the increase in reactive astrocytes around the infarcted area and at the edge of the proximal infarcted area. Yu et al. [62] found that pre-exposure to EE reduces the mRNA levels of iNOS and nNOS after MCAO, thus reducing inflammation, and that this reduction may be related to blocking the activation of ERK1/2 in microglia [63]. These studies indicate that the protective effect of EE on cerebral ischemia may inhibit POCD caused by CPB during cardiac surgery.

EE has been suggested to increase cerebral angiogenesis and reduce the expression of oxidative stress-related and apoptotic enzymes in the brain in an AD model [40]. EE may prevent the developmental loss of parvalbumin-immunoreactive cells in the prefrontal cortex induced by juvenile hypoxia and reduce neurobehavioral changes by inhibiting oxidative stress derived from NOX2 (NADPH oxidase 2). Moreover, EE significantly reduced the anxiety-like behaviors induced by daily intermittent hypoxia [63].

The Influence of Voluntary Exercise in EE

Studies have revealed that voluntary exercise in EE increases the thickness of the motor cortex and the expres-

sion of trophic factors such as BDNF, NGF, and FGF in the brain. Falkenberg et al. [64] found that the BDNF mRNA level in the hippocampus of rats increased and spatial memory was improved after EE. Dahlqvist et al. [65] proved that the social component of EE housing increases the expression of NGF mRNA in several cortical and hippocampal CA1 regions. Voluntary exercise also enhanced neurogenesis, related to the increase in exercise-induced IGF-1 uptake, in the hippocampus of adult animals [66]. Wadowska et al. [67] found that EE can enhance IGF-1 signaling through the Akt pathway and then reduce hippocampal neuronal loss and apoptosis after transient global cerebral ischemia. Intracerebroventricular injection of IGF also increased neurogenesis in the dentate gyrus of rats without increasing epidermal growth factor (EGF) or FGF-2 [68]. Voluntary exercise can also upregulate MKP-1, which plays an important role in the negative regulation of MAPK activation in proinflammatory macrophages [69].

The voluntary wheel-running associated with EE has been shown to provide protection against ischemia. In gerbils, providing a running wheel before surgery followed by 15 min of global cerebral ischemia reduced the mortality rate from 55 to 10%, and hippocampal cell damage was also reduced [70]. Voluntary exercise has also been shown to reduce inflammation and oxidative stress in the brain. The studies of Speisman et al. [71] on aged rats suggested that voluntary daily exercise on a running wheel reduced hippocampal IL-1 β and serum monocyte chemoattractant protein (MCP)-1 levels.

It has been found that both short- and long-term voluntary exercise in EE affects the expression of hippocampal genes; upregulation is observed in many genes, especially those related to the glutamatergic system, while genes related to the GABA system are downregulated [36]. Segovia et al. [72] found that the level of glutamate increased in the CA3 of aged rats after EE, and this increased the excitatory synaptic potential and LTP. Moreover, the increase in IGF-1R phosphorylation in animals exposed to EE indicates that EE can regulate injury-induced glutamate toxicity by reducing NMDAR1 phosphorylation [67]. Voluntary exercise can also affect cholinergic systems, such as choline uptake in the hippocampus and cortex, and enhance the activity of opioid systems [73]. In addition, monoamines, such as norepinephrine and serotonin, are activated by running or physical activity [74], which in turn increases synaptic plasticity and neurogenesis [45].

Effect of EE on Mechanisms Related to AD

Studies have indicated that AD11 mice, which show progressive behavioral impairment, provided with EE be-

fore the onset of behavioral impairment have preserved visual recognition memory and spatial memory. Long-term EE prevents the loss of cholinergic neurons in the forebrain, which may be related to the increased expression of neurotrophins, especially NGF and BDNF, in the target area of basal forebrain projections. In addition, in AD11 mice, exposure to EE reduced the presence of A β clusters in the hippocampus [75]. Hu et al. [76] demonstrated that EE could also reduce the hyperphosphorylation of Tau protein. These studies suggest that EE can effectively reduce and prevent the occurrence of AD at the molecular level and that such molecular mechanisms may also act on POCD, thereby inhibiting its occurrence and development. Some studies have also evaluated the effect on elderly subjects of participating in activities with cognitive requirements and found that the activities with higher cognitive requirements reduced the risk of developing AD [77].

Conclusion

POCD is a common postoperative brain complication that greatly reduces cognitive ability, such as memory, attention, and the execution of tasks, and it has an enormous impact on human life. The occurrence and development of POCD is closely related to advanced age, invasive surgery, duration of anesthesia, and level of education, and the main pathogenesis of POCD is neuroinflammation in the brain. HMGB1, IL-1, IL-6, TNF- α and inflammatory chemokines can promote POCD development. Hypoxia and oxidative stress in the brain and changes in the phenotype and receptor expression of microglia and astrocytes under inflammatory conditions also promote the occurrence of POCD. On the other hand, EE can affect the release and inhibition of related factors in the brain by enhancing novelty, social contact, and physical exercise, and thus improve the cognitive ability, memory, and other functions of the brain. EE can significantly increase synaptic transmission and plasticity in the hippocampus, and it enhances the release of trophic factors such as BDNF

and NGF so that the brain is more resistant to injury. EE also inhibits the release of inflammatory cytokines and chemokines in the brain, promotes the enhancement of cholinergic and glutamatergic activities and the inhibition of the GABA system, and negatively regulates the occurrence and development of POCD. These findings suggest that EE could be used as an effective preventive and therapeutic measure for POCD. However, the specific effect of EE can only be accurately determined after improving the evaluation criteria of POCD. Meanwhile, the molecular changes regulated by EE can also provide ideas for drug therapy targets. However, there are experimental shortfalls that reduce the translation of research results to humans. We should therefore retain a focus on preclinical research to promote progress in disease research. For example, we could explore the influence of the upstream targets of cytokines and chemokines, such as IGF-I or FGF-2, on the progression of POCD in EE.

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Conflict of Interest Statement

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Author Contributions

M.H. completed the whole work of this manuscript, including searching the literature, writing, and drawing the figure. J.M. is responsible for the revision of grammar and the improvement of sentences.

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