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REVIEW ARTICLE

Postoperative cognitive dysfunction in the aged: the collision of neuroinflammaging with perioperative neuroinflammation

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Abstract

The aging population is burgeoning globally and this trend presents great challenges to the current healthcare system as the growing number of aged individuals receives procedures of surgery and anesthesia. Postoperative cognitive dysfunction (POCD) is a severe postoperative neurological sequela. Advanced age is considered as an independent risk factor of POCD. Mounting evidence have shown that neuroinflammation plays an essential role in POCD. However, it remains debatable why this complication occurs highly in the aged individuals. As known, aging itself is the major common high-risk factor for age-associated disorders including diabetes, cardiovascular disease, cancer, and neurodegenerative diseases. Chronic low-grade neuroinflammation (dubbed neuroinflammaging in the present paper) is a hallmark alternation and contributes to age-related cognitive decline in the normal aging. Interestingly, several lines of findings show that the neuroinflammatory pathogenesis of POCD is age-dependent. It suggests that age-related changes, especially the neuroinflammaging, are possibly associated with the postoperative cognitive impairment. Understanding the role of neuroinflammaging in POCD is crucial to elucidate the mechanism of POCD and develop strategies to prevent or treat POCD. Here the focus of this review is on the potential role of neuroinflammaging in the mechanism of POCD. Lastly, we briefly review promising interventions for this neurological sequela.

Keywords POCD · Aging · Neuroinflammation · Surgery · Anesthesia

Introduction

A syndrome of prolonged cognitive impairment after anesthesia and surgery is described as postoperative cognitive dysfunction (POCD). It is characterized by a disturbance in memory, intellectual ability, and executive function (Hanning 2005; Moller et al. 1998; Newfield 2009). POCD may follow postoperative delirium (POD) and develop into mild cognitive impairment and even dementia (Sprung et al. 2017; Steinmetz et al. 2009). And now POCD and POD are both recommend to be named postoperative neurocognitive disorder (Evered et al. 2018). It is well established that advanced age is the most significant risk factor for POCD after non-cardiac major surgery (Kubota et al. 2018; Monk et al. 2008; Sprung et al. 2017). As known, aging is a natural process and with the development of healthcare system burgeoning aged population is an inevitable trend. Therefore, there is a considerable increase in the number of the elderly individuals receiving procedures of surgery and anesthesia, which poses new challenges to the current healthcare system.

A wealth of preclinical studies have been emerged to explore the biological pathophysiological mechanism involved in POCD (Hovens et al. 2012; Newfield 2009; Skvarc et al. 2018; Terrando et al. 2015a; Vacas et al. 2017). Although there is no unanimous agreement with the mechanism of POCD, neuroinflammation gives us insights into investigating this postoperative sequela (Cao et al. 2010; Hovens et al. 2014; Skvarc et al. 2018; Terrando et al. 2016; Vacas et al. 2013; Wan et al. 2010). Neuroinflammation is

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involved in conditions of brain disorders as well as normal aging. Interestingly, the low-degrade neuroinflammation in normal aging, dubbed neuroinflammaging in the present paper, is one hallmark change in the brain aging (Lopez-Otin et al. 2013). Neuroinflammaging is revealed by disruption of blood–brain barrier (BBB), microglial activation, A1-like astrocytes, and low-grade increase of inflammatory cytokines (Barrientos et al. 2015; Clarke et al. 2018; Montagne et al. 2015; Schuitemaker et al. 2012). These age-related alternations contribute, at least partially, to the age-related cognitive decline in the aged individuals or models (Bettio et al. 2017; Harry 2013; Montagne et al. 2015; Rawji et al. 2016). Regarding to the role neuroinflammaging in the POCD, there is no evidence that definitely demonstrated neuroinflammaging is involved in POCD in the aged experimental models or individuals, but the findings that the occurrence of POCD is age-dependent (Bi et al. 2017; Hovens et al. 2015; Xu et al. 2014; Yang et al. 2017) indirectly suggest age-related alternations is correlated with pathogenesis of POCD in the aged. Therefore, the main objectives of this paper are to delve into the currently available findings that suggest age-related changes, neuroinflammaging in particular, contribute to POCD of aged subjects. Simultaneously, we generally summarize the role of neuroinflammation in POCD and briefly outline the promising measurement for this neurological complication following the surgical procedure.

Neuroinflammation in POCD

Because previous studies reported that increasing age was the independent risk factor of POCD (Cao et al. 2010; Kubota et al. 2018; Monk et al. 2008; Zhao et al. 2016), the present review is focused on aged models. As known, clinical anesthesia has been shown to minimize the stress response to perioperative invasive procedures. Therefore, investigations pertaining to the sole role of general anesthetics in POCD were not recruited in this section. On the other hand, some general anesthetics are immuno-modulators (Stollings et al. 2016) and it is still a matter of debate whether general anesthetics-mediated immunomodulation is involved in POCD. However, increasing data supports the argument that anesthesia and surgery are not the risk factors for the postoperative cognitive decline after non-cardiac major surgery (Evered et al. 2011; Hughes et al. 2017). This suggests that immunomodulation by general anesthetics is unlikely to be an initiator of activating the neuroinflammatory cascade in POCD. Together, the principal focus of this section was on seeking the role of neuroinflammation in aged POCD models.

Extensive studies are aimed at elucidating the exact mechanism of pathogenesis of POCD, but it is likely correlated with multitudinous factors of neurophysiological changes, among which activated neuroinflammatory response is the most significantly concerned. The mechanism underlying neuroinflammation in POCD includes excessive release of cytokines (Cibelli et al. 2010; Hu et al. 2018; Terrando et al. 2010; Wan et al. 2007), activation of the glial cell (Hovens et al. 2015; Rosczyk et al. 2008; Wan et al. 2010), disruption of blood–brain barrier (BBB) (Cao et al. 2010; Li et al. 2016b; Yang et al. 2017; Zheng et al. 2017), invasion of peripheral immune cells into the central nervous system (CNS) (Degos et al. 2013; Hovens et al. 2015; Vacas et al. 2014), and delayed resolution of postoperative neuroinflammation (Terrando et al. 2011; Vacas et al. 2013). Among these mechanisms, microglial priming is usually considered as the main culprit of POCD as microglia are at the nexus of crosstalk between neuroinflammation and abnormal neuronal functioning, neuroapoptosis and synaptic injury (Barrientos et al. 2012; Cao et al. 2010; Hovens et al. 2015; Qiu et al. 2016; Skvarc et al. 2018). Accumulating data showed that various perioperative injury factors, such as excessive production of inflammatory cytokines and reactive oxygen species, imbalance of cerebral iron metabolism, and down-regulated type 2 cannabinoid receptors could induce microglial activation (Cibelli et al. 2010; Hovens et al. 2014, 2015; Hu et al. 2018; Li et al. 2016a; Qiu et al. 2016; Skvarc et al. 2018; Sun et al. 2017; Terrando et al. 2010; Zheng et al. 2017). In turn, activated microglia produced more injury factors and exacerbated injurious process. In other word, it forms a vicious cycle and ultimately lead to postoperative neurological sequela (Figure 1, online resource). Taken together, neuroinflammation, in particular involved with microglia priming, plays a pivotal role in pathophysiological mechanism of POCD in the aged.

However, to our knowledge, there are two controversial topics in this field. The first one is that the neuroinflammatory response even the microglial priming does not always mean cognitive injury. It is seems stage-specific in the completely pathological process of neurodegeneration (Sochocka et al. 2017). Coincidentally, an unexpected clinical finding showed a profound decrement of glial activity 3–4 days after patients received robotic prostatectomy (Forsberg et al. 2017). This was the first study found postoperative immunosuppression was correlated with postoperative cognitive impairment. It was unclear this immunosuppressive phenomenon was primary response or secondary response to the initial perioperative "cytokine storm".

The second one is where is the initial change of inflammatory cytokines, peripheral or intracerebral? Given that pure intracerebral cytokines initiate neuroinflammation, measurements neutralizing the peripherally proinflammatory cytokines may not offer improvement in cognition. In contrast, preclinical findings showed that peripheral blockade of proinflammatory cytokines did mitigate the

cognitive impairment of the models subject to orthopedic surgery (Cibelli et al. 2010; Hu et al. 2018; Terrando et al. 2010). Of interest, intracisternal administration of interleukin (IL)-1 receptor antagonist or tumor necrosis factor (TNF)-α receptor antagonist also alleviated postoperative cognitive decline in aged rodent models (Barrientos et al. 2012; Ma et al. 2015). Of note, a study found that surgery aggravated preoperative existed neuroinflammation, revealed by pronounced growing level of TNFα and IL-6, but did not correspondingly worsen the cognitive injury (Vacas et al. 2017). Surprisingly, the authors pointed out that the existed neuroinflammation was associated with the postoperative cognitive decline. There is a possibility that surgery-induced neuroinflammation did not reach the intensity to result in a detectable impairment in cognitive performance, because surgery itself does not causally associated with cognitive deficit (Hughes et al. 2017). Considering the communication between peripheral immune system and CNS, the comprised function and integrity of blood–brain barrier in POCD should not be neglected. In line with this argument, it was observed in several studies that the integrity of BBB was impaired via different molecular mechanisms in aged POCD models (Bi et al. 2017; He et al. 2012; Terrando et al. 2016; Wang et al. 2017a; Yang et al. 2017; Zheng et al. 2017; Zhu et al. 2018). These data present new challenge for further investigating the origin of inflammatory response in POCD. In light of the current evidence, it is difficult to draw a conclusion from which is the proinflammatory cytokines originally derived.

As mentioned before, advancing age is unanimously proposed as the independent risk factor for POCD in preclinical (Bi et al. 2017; Wang et al. 2018; Xu et al. 2014; Yang et al. 2017) and clinical findings (Kubota et al. 2018; Moller et al. 1998; Monk et al. 2008). Thus, we came up a hypothesis that any aging-related changes contributed to the POCD in the aged. In next section, we attempted to evaluate this hypothesis based on the current evidence.

Neuroinflammaging and its emerging role in POCD

Neuroinflammaging

Aging is the inevitable process of living organisms and characterized by a progressive loss of physiological integrity and functional decline of organs.

During aging process, every system of the body undergoes various adaptive changes that increase the vulnerability to insult. Indeed, it is widely accepted that aging is the major common risk factor for frailty, decreased physical resilience as well as chronic diseases, which include neurodegenerative diseases, heart diseases, cancer and so on (Barzilai et al. 2018; Tchkonia and Kirkland 2018). One important molecular mechanism underlying these diseases is revealed by chronic, sterile, and low-grade increase of inflammation that may not be beyond the physiological range (Fulop et al. 2014; Lopez-Otin et al. 2013; Rawji et al. 2016). This phenomenon is termed as "inflammaging" (Franceschi et al. 2000; Franceschi and Campisi 2014; Vasto et al. 2007). Of great interest, a chronic, low-level increase of inflammation together with glial activation was found in the normal aging brain (Barrientos et al. 2015; Bettio et al. 2017; Norden and Godbout 2013). This phenomenon is dubbed "neuroinflammaging" in several previous studies (Davinelli et al. 2016; Grinan-Ferre et al. 2016; Lana et al. 2016). Until now, the term "neuroinflammaging" may be just referred to the nomenclature of "inflammaging" and not universally used in published literatures. In the present review, we used this term as an abbreviation in the context with inflammation in the normal aging brain.

In the setting of physiological aging, there is a nuanced balance between neuroinflammaging and neuronal functioning. However, this fragile homeostasis is easily interrupted when individuals are subject to pathological insults (Bettio et al. 2017). In fact, the homeostatic disturbance of neuroinflammaging was observed in the pathophysiological mechanisms of neurodegenerative diseases (Bettio et al. 2017; Di Benedetto et al. 2017; Liang et al. 2017; Pizza et al. 2011). Accumulating findings suggested that even neurologically asymptomatic aged individuals demonstrated neuroinflammaging as chronic, low-grade increase of neuroinflammatory mediators, progressive glial activation and partial collapse of BBB (Lopez-Otin et al. 2013). Therefore, we hypothesized that the collision of preoperative existed neuroinflammaging with perioperative neuroinflammatory response was key point to address the conundrum in the pathological mechanism of POCD in the old subject (Figure 2, online resource). In the next section, we focus on the elements associated with neuroinflammaging and their potential role in POCD of the elderly.

Aging BBB and its role in POCD

BBB, composed of cerebral endothelial cells, perivascular mural cells and pericytes, is a firewall which curtails the entry of the peripheral neurotoxic substance into brain, keeps a homeostatic "milieu'' for normal neuronal functioning, and reserves proper channels to communicate with other system outside of the brain (Ballabh et al. 2004). In a traditional perspective, brain was once thought as an immune-privileged organ. The brain and the peripheral immune system were isolated by a relatively impenetrable BBB. However, the recognition on the communication between the brain and the immune system has overwhelmingly changed because of the amazing advance in the interplay of

brain-immune modulation (Ellwardt et al. 2016; Louveau 2015a, b, 2017). Accordingly, it is now widely accepted that CNS and the immune system continuously interact with each other in the context of physiological as well as pathological context throughout the lifespan (Di Benedetto et al. 2017; Liang et al. 2017; Schwartz et al. 2013).

However, BBB usually bears the brunt of pathological insults since it is the interface of peripheral immune system and brain. It is, therefore, not surprising that BBB damage is found in extensive studies of neurodegenerative diseases (Erdo et al. 2017; van de Haar et al. 2015; Zlokovic 2008). It remains controversial whether BBB leakage occurs in normal aging of human until Montagne et al (2015) validated this striking hypothesis. The evidence showed that BBB breakdown occurred in the early period of brain aging and initiated in the hippocampus. It is noteworthy that increased permeability of hippocampal BBB coincides with exacerbated mild cognitive impairment (Montagne et al. 2015). Together, this suggests that loss of cerebrovascular integrity of BBB during normal aging contributes to early onset of cognitive deficit.

It is our principal concern whether BBB is involved in POCD in the aged models or individuals in the present review. As expected, mounting data showed that BBB was disrupted in POCD of aged rodent models receiving different surgery even only anesthetics exposure (Cao et al. 2018; He et al. 2012; Li et al. 2016b; Ni et al. 2018; Yang et al. 2017; Zheng et al. 2017). It seems that different molecular mechanism involved in the disruption of BBB following surgery and anesthesia (Bi et al. 2017; Cao et al. 2018; He et al. 2012; Li et al. 2016b; Ni et al. 2018; Zheng et al. 2017). As BBB became leakier, various perioperative insults may promote neurotoxic factors into CNS and further deteriorate preexisting low-grade neuroinflammation of normal aging that eventually results in cognitive impairment in the aged models. This notion was supported by the findings the disruption of BBB after surgery and anesthesia was age-dependent (Bi et al. 2017; Yang et al. 2017). It means aging BBB is susceptible to damage in the aged POCD models. An elaborate research provide indirect evidence that age-related BBB injury was possibly associated with peripheral inflammation-induced cognitive dysfunction (Zhu et al. 2018). Taken together, the increased permeability of BBB in normal aging possibly contributes to POCD in the aged models.

Aging microglia and its role in POCD

As a unique population of immune cells resident in the brain, microglia are associated with a variety of in physiological and pathological setting in development and neurodegenerative diseases (Harry 2013; Salter and Stevens 2017). They participate in neuroplasticity by synaptic pruning and secretion of neurotrophic factors in the development of brain (Harry 2013). Meanwhile, they are involved with synaptic loss and tau propagation in age-related neurodegenerative diseases (Salter and Stevens 2017). Once activated by nocuous stimuli, microglia become amoeboid in morphology and polarized in phenotype. Of note, a subset of dark microglia was described as hyperactive microglia with condensed cytoplasm and postulated to be predominantly associated with pathological remodeling of neural network (Bisht et al. 2016).

During normal aging, the age-related changes in glial cells are prior to those in neurons (Soreq et al. 2017). Moreover, interventions targeting senescent glial cells mitigated tau-mediated pathologies (Bussian et al. 2018). These data suggested that senescent glial cells play an important role in the initiation and progression of age-related neurodegeneration. In normal aging, microglia are prone to change into a more primed state that is associated with the increased proinflammatory profiles in the brain (Grabert et al. 2016; Li and Barres 2017; Schuitemaker et al. 2012). It showed that microglial phenotype became de-ramified and was comparable to activated ones in the brain of aged rodents. The primed microglia was postulated to be associated with age-related augmented neuroinflammation, reduced neurogenesis, synaptic aberrations and hence cognitive impairment (Salter and Stevens 2017). In summary, age-related microglial priming may be the underlying mechanism of age-related neurodegeneration.

There has been an explosion of findings recently giving us insights into the involvement of neuroinflammation in POCD of the aged models. As the resident immune cells of the CNS, microglia are endowed with the natural advantage to take center stage in research for their roles in the origin of neuroinflammatory cytokines in aged POCD models. A host of studies have found that microglia were activated in hippocampi of aged rodents, resulting in excessive release of neuroinflammatory cytokines in the brain (Hovens et al. 2014, 2015; Qiu et al. 2016; Rosczyk et al. 2008; Vacas et al. 2013). Interestingly, a study observed that microglia activation was region-specific in old rats subject to procedure of major abdominal surgery and those activated in hippocampi contributed to deficit in spatial memory in the MWM probe trial (Barrientos et al. 2015). Indeed, activated microglia was found in some areas of brain including frontal lobe, cingulate cortex, entorhinal cortex, as well as hippocampus in the normal aging (Schuitemaker et al. 2012). One hallmark alternation of the aging brain is the chronically, low-grade increased neuroinflammation (Lopez-Otin et al. 2013). It remains a matter of debate whether activated microglia is the original resource of low-grade neuroinflammation in normal aging, but it is definite age-related neuroinflammation increased the susceptibility to cognitive impairments following an immune challenge such as infection, traumatic brain

injury, or perioperative stress (Barrientos et al. 2015; Bettio et al. 2017). Concerning POCD, there are indirect evidence that the intensity of neuroinflammation is age-dependent in animal models (Hovens et al. 2015; Yang et al. 2017; Zheng et al. 2017). However, it is unknown whether is casual link between aged-related microglial activation and postoperative cognitive impairment in the aged models. Further work need to carry out to validate this hypothesis.

Aging astrocytes and its role in POCD

Astrocytes are the largest group of glial cells in the CNS. They were once considered as support cells in healthy CNS and passive responders even bystander to neuronal injury in disease, but now it is widely accepted that they carry out a variety of essential functions in the brain under healthy or pathological conditions (Ben Haim and Rowitch 2017; Dallerac and Rouach 2016; Sofroniew 2014; Sofroniew and Vinters 2010). Under physiological condition, astrocytes are proposed to be one side of "tripartite" synapses and active drivers of neuron-astrocyte communication so that modulate synaptic function and integration of neural circuits (Perea et al. 2009; Stogsdill et al. 2017). With the harmful stimuli, activated astrocytes are postulated to be associated with synaptic and cognitive impairment in neurodegenerative and psychiatric disorders (Chung et al. 2015; Dallerac and Rouach 2016). Therefore, reactive astrocytes are suggested as potential target for prophylaxis or treatment of CNS disorders.

With regard to the process of in aging, astrocytes show molecular and structural phenotype. The structural changes present as alternation in processes, which become shorter and stubbier with aging (Castiglioni et al. 1991; Jyothi et al. 2015; Soreq et al. 2017). With respect to molecular profile of changes, aged astrocytes showed various alternation. Notably, glial fibrillary acidic protein was found increase in aged astrocytes (Cerbai et al. 2012; Kohama et al. 1995) and this finding that astrocytes become reactive with aging. A recent finding that aged astrocytes showed characteristics of A1 reactive astrocyte (a toxic subtype) supported this notion (Clarke et al. 2018). Furthermore, regulatory gene for behavioral ageing 1 from aged glia accelerated behavioral deterioration by activating mitochondrial unfolded protein response in neurons of *C. elegans* (Yin et al. 2017). More importantly, several studies suggested that astrocyte and microglia interacted in a complex manner in aging and pathological situation. The time points of microglial alteration with aging were similar to those of astrocytes' (Soreq et al. 2017). Strikingly, primed microglia induced neurotoxic A1 astrocytes, which was predominantly present in neurodegenerative disease (Liddelow et al. 2017). This process was dependent on a cluster of cytokines, IL-1α, TNF, and complement C1q. During normal aging, there was no significantly increase in A1 astrocytes-related genes in mice lacking the microglia-derived IL-1α, TNF, and C1q (Clarke et al. 2018). This suggests that aged microglia promote A1 astrocytes activation in normal aging. Since A1 astrocytes lose their physiological function, but by contrast, release neurotoxic factor to neurons and oligodendrocytes, the properties of A1 astrocytes probably contribute to the normal aging-related cognitive decline and increase the vulnerability of brain to hazard insults.

As neuroinflammation plays a critical role of in neurodegeneration and microglia are the unique brain-resident macrophages, most of the research focused on investigating the role of microglia in POCD of the elderly. However, there was still fewer attention that was payed to examining the role of astrocytes in this neurological complication after surgery and anesthesia (Wan et al. 2007, 2010; Xu et al. 2017; Zhang et al. 2016). It is no finding that A1 astrocytes take part in neuroinflammation in the POCD in the aged models. Strikingly, a recent study showed that C3/C3a receptor signaling was activated and contributed cognitive impairment after orthopedic surgery in adult mice (Xiong et al. 2018). Release C3a is one characteristic of A1 astrocytes formation (Liddelow et al. 2017). These findings provide the possibility that astrocytes in normal aging may contribute to, at least partially, cognitive decline in the aged models after surgery. Moreover, further studies need to be undertaken to examine the exact role of aged astrocyte in POCD.

Potential interventions

Anti-neuroinflammatory strategies

In light of the close association of neuroinflammation and postoperative neurological performance in POCD, anti-neuroinflammatory strategies are usually preferentially considered to prevent or treat this complication.

A series of the potential strategies that targeted neuroinflammation to prevent or treat POCD, as well as their corresponding mechanisms, are summarized in Table 1 (online resource).

NSAIDs

Several nonsteroidal anti-inflammatory drugs (NSAIDs), such as parecoxib, ibuprofen, and acetaminophen were found to mitigate neuroinflammation and improve cognitive function. As known, parecoxib is a high-selective cyclooxygenase (COX) 2 inhibitor and reported to have sufficient distribution in the CNS. Animal models and clinical subject of administered by parecoxib showed better-preserved cognitive performance. The neuroprotective effect was mediated by downregulating the expression of IL-1β and TNF-α in the

brain (Gong et al. 2012; Peng et al. 2012; Zhu et al. 2016b). Unlike parecoxib, ibuprofen is an inhibitor of both COX 1 and COX 2. Ibuprofen produces analgesic, antipyretic, and anti-inflammatory effect by inhibiting COX 2 (Kakuta et al. 2008). Studies in preclinical and clinical settings have showed that ibuprofen improved postoperative cognitive function (Huang et al. 2018; Le 2016). A recent study showed that acetaminophen significantly downregulated L-1 β, IL-6, and TNF-α in hippocampi of mice and improved cognitive performance (Zhao et al. 2017). Together, these findings suggest that perioperative commonly used NSAIDs are promising agents to prevent or treat POCD.

Dexmedetomidine

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist. It is first licensed to use in sedation and now admitted to use in anesthesia maintaining in clinical anesthesia (Hoy and Keating 2011). In tibial fracture model, dexmedetomidine treatment reduced the expression of IL-1β, IL-6, and TNF-α and inhibited the activation of astrocytes and microglia in hippocampi (Paeschke et al. 2017; Zhu et al. 2016a). In clinical settings, dexmedetomidine was showed to improve the short-term and long-term cognitive function in the elderly admitted to the intensive care unit after non-cardiac surgery (Su et al. 2016; Zhang et al. 2018). Furthermore, a recent meta-analysis supported this hypothesis (Duan et al. 2018). However, there is conflicted finding that intraoperative infusion dexmedetomidine did not prevent postoperative delirium and cognitive dysfunction in elderly individuals (Deiner et al. 2017). It is likely that the neuroprotection of dexmedetomidine is dependent on its dosage and timing of administration in the clinical context. To sufficiently explore the promising effect of dexmedetomidine, more concern needs to be focused on optimizing the administration regimen.

Minocycline

Minocycline is a second-generation tetracycline. It has been shown to exert both antimicrobial and anti-inflammatory action (Yrjanheikki et al. 1999). It can easily cross the BBB and provide neuroprotective effect against insults associated with aggravated neuroinflammatory response, including cerebral ischemia, Alzheimer disease, and neuropathy in diabetes (Ferretti et al. 2012; Jalal et al. 2015; Vincent and Mohr 2007). In line with this argument, mounting preclinical evidence showed that minocycline provided the promising neuroprotection against this postoperative cognitive impairment by modulating the levels of proinflammatory cytokines and the activity of microglia (Cibelli et al. 2010; Kong et al. 2013; Li et al. 2013; Sun et al. 2017). However, it needs to be further examine whether minocycline is effective in the prevention of POCD in clinical context.

Ulinastatin

It is identified as a urinary trypsin inhibitor, and widely used in patients with inflammatory disorders. In clinical trials, ulinastatin was observed to lower IL-6 and S100beta concentrations up to postoperative day 2 and improve the MMSE score on day 1, day 3, and day 7 after operation (Lv et al. 2016; Wang et al. 2017b).

Other anti-neuroinflammatory measurements

Pretreatment with deferoxamine suppressed microglial activation, oxidative stress, and inflammatory response and improved cognitive function in rodent models of POCD (Li et al. 2016a; Pan et al. 2016). In addition, it was reported interventions activating SIRT3 (Ye et al. 2018), cannabinoid receptor type 2 (Sun et al. 2017), TREM2 (Jiang et al. 2018) and α7 nicotinic acetylcholine receptor (Kong et al. 2015; Terrando et al. 2015b) showed anti-neuroinflammatory effect and mitigated cognitive decline in the old POCD models.

Physical strategies

Another encouraging measurement for POCD is to explore natural anti-inflammatory methods, including dietary restriction, physical exercise and environmental enrichment. Actually, robust data demonstrate that dietary restriction can prevent the age-related cognitive decline even increase lifespan expectancy in different species (Cohen et al. 2004; Fontana et al. 2010). Despite the compelling evidence undergirding the effectiveness of dietary restriction to improve age-related cognitive function, it is tough for most individuals to maintain this harsh dietary style for the long run. Besides the dietary restriction method, the practice of physical activity is also correlated to cognitive improvement in the aging individuals (Hillman et al. 2008). The beneficial effect of physical exercise on brain function is mediated by complex neuro-immuno-endocrine modulation (Gambus et al. 2015; Trivino-Paredes et al. 2016). The previous findings indicated that rats with low exercise endurance showed persistent memory deficit compared to those with high exercise endurance (Feng et al. 2013; Gambus et al. 2015). Environmental enrichment is an alternate strategy of cognitive stimulation and can improve hippocampal-dependent spatial memory in preclinical studies (Schloesser et al. 2010). Of note, preoperative environmental enrichment reduced cognitive impairment by inhibiting hippocampal neuroinflammation and age-related microglial phenotype in aged rats after abdominal surgery (Kawano et al. 2015).

The notion that these physical measurements are effective in improving cognitive function is summarized from the preclinical data. It remain elusive whether they work in the individuals of high risk of POCD. Therefore, more

investigations should be carried out to examine whether they could provide a beneficial effect to older individuals with high risk of POCD and the potentially biological mechanism.

Others

Several studies show that polyphenols or antioxidants can reduce cognitive impairment in the aged models of POCD (Gogenur et al. 2007; Li et al. 2014; Wu et al. 2017), but they need to be tested in the clinical settings. In addition, gut microbiota, supposed to have extensive physiological and pathological function, was observed that could modulate microglia and neuroinflammation (Sampson et al. 2016; Thion et al. 2018; Vaiserman et al. 2017). Amazingly, two recently published studies showed that the prophylactic effect of excise on postoperative neuroinflammation and cognitive impairment was modulated by gut microbiome (Feng et al. 2017; Zhan et al. 2018). These findings pave an attractive way to prevent and treat by intervention gut microbiome. In addition, the feasibility and effectiveness of this method need to be examined in the clinical background.

Conclusions

Aging is a natural, but irreversible, process of life and inevitably concomitant with decline of body system. With the rapid worldwide growing in aging population and advance in medical technology, POCD, a severe neurological complication with high occurrence in the elderly population, received explosive interest of experts from perioperative medicine. Advanced age is an independent risk factor of POCD, suggesting age-associated changes may be involved in its pathogenesis. Neuroinflammaging manifests as low-grade neuroinflammation, microglial activation, BBB disruption, and A1-like astrocytes, some of which were also observed in the aged POCD models. Given that neuroinflammaging contributes to age-related cognitive decline, the pre-existed neuroinflammaging in the aged individuals possibly increases the susceptibility to postoperative stress. And that the outcome might display as deteriorating cognitive performance in postoperative period. This opens a possibility to elucidate pathophysiological mechanism of POCD from the perspective of combining basic condition of individuals with the perioperative stress. Furthermore, strategies that delay or counteract neuroinflammaging may pave a way to prevent or treat POCD in the aged population.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

References

Ballabh P, Braun A, Nedergaard M (2004) The blood–brain barrier: an overview: structure, regulation, and clinical implications. Neurobiol Dis 16:1–13. https://doi.org/10.1016/j.nbd.2003.12.016

Barrientos RM, Hein AM, Frank MG, Watkins LR, Maier SF (2012) Intracisternal interleukin-1 receptor antagonist prevents postoperative cognitive decline and neuroinflammatory response in aged rats. J Neurosci 32:14641–14648. https://doi.org/10.1523/JNEUROSCI.2173-12.2012

Barrientos RM, Kitt MM, Watkins LR, Maier SF (2015) Neuroinflammation in the normal aging hippocampus. Neuroscience 309:84–99. https://doi.org/10.1016/j.neuroscience.2015.03.007

Barzilai N, Cuervo AM, Austad S (2018) Aging as a biological target for prevention and therapy. JAMA. https://doi.org/10.1001/jama.2018.9562

Ben Haim L, Rowitch DH (2017) Functional diversity of astrocytes in neural circuit regulation. Nat Rev Neurosci 18:31–41. https://doi.org/10.1038/nrn.2016.159

Bettio LEB, Rajendran L, Gil-Mohapel J (2017) The effects of aging in the hippocampus and cognitive decline. Neurosci Biobehav Rev 79:66–86. https://doi.org/10.1016/j.neubiorev.2017.04.030

Bi J, Shan W, Luo A, Zuo Z (2017) Critical role of matrix metallopeptidase 9 in postoperative cognitive dysfunction and age-dependent cognitive decline. Oncotarget 8:51817–51829. https://doi.org/10.18632/oncotarget.15545

Bisht K et al (2016) Dark microglia: a new phenotype predominantly associated with pathological states. Glia 64:826–839. https://doi.org/10.1002/glia.22966

Bussian TJ, Aziz A, Meyer CF, Swenson BL, van Deursen JM, Baker DJ (2018) Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. Nature 562:578–582. https://doi.org/10.1038/s41586-018-0543-y

Cao XZ et al (2010) Postoperative cognitive deficits and neuroinflammation in the hippocampus triggered by surgical trauma are exacerbated in aged rats. Prog Neuropsychopharmacol Biol Psychiatry 34:1426–1432. https://doi.org/10.1016/j.pnpbp.2010.07.027

Cao Y et al (2018) Hypoxia-inducible factor-1α is involved in isoflurane-induced blood–brain barrier disruption in aged rats model of POCD. Behav Brain Res 339:39–46. https://doi.org/10.1016/j.bbr.2017.09.004

Castiglioni AJ, Legare ME, Busbee DL, Tiffany-Castiglioni E (1991) Morphological changes in astrocytes of aging mice fed normal or caloric restricted diets. Age 14:102–106. https://doi.org/10.1007/BF02435015

Cerbai F et al (2012) The neuron-astrocyte-microglia triad in normal brain ageing and in a model of neuroinflammation in the rat hippocampus. PLoS ONE 7:e45250. https://doi.org/10.1371/journal.pone.0045250

Chung WS, Welsh CA, Barres BA, Stevens B (2015) Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci 18:1539–1545. https://doi.org/10.1038/nn.4142

Cibelli M et al (2010) Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 68:360–368. https://doi.org/10.1002/ana.22082

Clarke LE, Liddelow SA, Chakraborty C, Munch AE, Heiman M, Barres BA (2018) Normal aging induces A1-like astrocyte reactivity. Proc Natl Acad Sci USA 115:E1896–E1905. https://doi.org/10.1073/pnas.1800165115

Cohen HY et al (2004) Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 305:390–392. https://doi.org/10.1126/science.1099196

Dallerac G, Rouach N (2016) Astrocytes as new targets to improve cognitive functions. Prog Neurobiol 144:48–67. https://doi.org/10.1016/j.pneurobio.2016.01.003

Davinelli S, Maes M, Corbi G, Zarrelli A, Willcox DC, Scapagnini G (2016) Dietary phytochemicals and neuro-inflammaging: from mechanistic insights to translational challenges. Immun Ageing 13:16. https://doi.org/10.1186/s12979-016-0070-3

Degos V et al (2013) Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. Anesthesiology 118:527–536. https://doi.org/10.1097/ALN.0b013e3182834d94

Deiner S et al (2017) intraoperative infusion of dexmedetomidine for prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. JAMA Surg 152:e171505. https://doi.org/10.1001/jamasurg.2017.1505

Di Benedetto S, Muller L, Wenger E, Duzel S, Pawelec G (2017) Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. Neurosci Biobehav Rev 75:114–128. https://doi.org/10.1016/j.neubiorev.2017.01.044

Duan X, Coburn M, Rossaint R, Sanders RD, Waesberghe JV, Kowark A (2018) Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth 121:384–397. https://doi.org/10.1016/j.bja.2018.04.046

Ellwardt E, Walsh JT, Kipnis J, Zipp F (2016) Understanding the role of T cells in CNS homeostasis. Trends Immunol 37:154–165. https://doi.org/10.1016/j.it.2015.12.008

Erdo F, Denes L, de Lange E (2017) Age-associated physiological and pathological changes at the blood–brain barrier: a review. J Cereb Blood Flow Metab 37:4–24. https://doi.org/10.1177/0271678X16679420

Evered L, Scott DA, Silbert B, Maruff P (2011) Postoperative cognitive dysfunction is independent of type of surgery and anesthetic. Anesth Analg 112:1179–1185. https://doi.org/10.1213/ANE.0b013e318215217e

Evered L et al (2018) Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. Br J Anaesth 121:1005–1012. https://doi.org/10.1016/j.bja.2017.11.087

Feng X et al (2013) Surgery results in exaggerated and persistent cognitive decline in a rat model of the Metabolic Syndrome. Anesthesiology 118:1098–1105. https://doi.org/10.1097/ALN.0b013e318286d0c9

Feng X, Uchida Y, Koch L, Britton S, Hu J, Lutrin D, Maze M (2017) Exercise prevents enhanced postoperative neuroinflammation and cognitive decline and rectifies the gut microbiome in a rat model of metabolic syndrome. Front Immunol 8:1768. https://doi.org/10.3389/fimmu.2017.01768

Ferretti MT, Allard S, Partridge V, Ducatenzeiler A, Cuello AC (2012) Minocycline corrects early, pre-plaque neuroinflammation and inhibits BACE-1 in a transgenic model of Alzheimer's disease-like amyloid pathology. J Neuroinflammation 9:62. https://doi.org/10.1186/1742-2094-9-62

Fontana L, Partridge L, Longo VD (2010) Extending healthy life span-from yeast to humans. Science 328:321–326. https://doi.org/10.1126/science.1172539

Forsberg A et al (2017) The immune response of the human brain to abdominal surgery. Ann Neurol 81:572–582. https://doi.org/10.1002/ana.24909

Franceschi C, Campisi J (2014) Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 69(Suppl 1):S4–9. https://doi.org/10.1093/gerona/glu057

Franceschi C, Bonafe M, Valensin S, Olivieri F, De Luca M, Ottaviani E, De Benedictis G (2000) Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 908:244–254

Fulop T, Le Page A, Fortin C, Witkowski JM, Dupuis G, Larbi A (2014) Cellular signaling in the aging immune system. Curr Opin Immunol 29:105–111. https://doi.org/10.1016/j.coi.2014.05.007

Gambus PL et al (2015) Relation between acute and long-term cognitive decline after surgery: influence of metabolic syndrome. Brain Behav Immun 50:203–208. https://doi.org/10.1016/j.bbi.2015.07.005

Gogenur I, Middleton B, Burgdorf S, Rasmussen LS, Skene DJ, Rosenberg J (2007) Impact of sleep and circadian disturbances in urinary 6-sulphatoxymelatonin levels, on cognitive function after major surgery. J Pineal Res 43:179–184. https://doi.org/10.1111/j.1600-079X.2007.00460.x

Gong M, Chen G, Zhang XM, Xu LH, Wang HM, Yan M (2012) Parecoxib mitigates spatial memory impairment induced by sevoflurane anesthesia in aged rats. Acta Anaesthesiol Scand 56:601–607. https://doi.org/10.1111/j.1399-6576.2012.02665.x

Grabert K et al (2016) Microglial brain region-dependent diversity and selective regional sensitivities to aging. Nat Neurosci 19:504–516. https://doi.org/10.1038/nn.4222

Grinan-Ferre C et al (2016) Behaviour and cognitive changes correlated with hippocampal neuroinflammaging and neuronal markers in female SAMP8, a model of accelerated senescence. Exp Gerontol 80:57–69. https://doi.org/10.1016/j.exger.2016.03.014

Hanning CD (2005) Postoperative cognitive dysfunction. Br J Anaesth 95:82–87. https://doi.org/10.1093/bja/aei062

Harry GJ (2013) Microglia during development and aging. Pharmacol Ther 139:313–326. https://doi.org/10.1016/j.pharmthera.2013.04.013

He HJ et al (2012) Surgery upregulates high mobility group box-1 and disrupts the blood–brain barrier causing cognitive dysfunction in aged rats. CNS Neurosci Ther 18:994–1002. https://doi.org/10.1111/cns.12018

Hillman CH, Erickson KI, Kramer AF (2008) Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci 9:58–65. https://doi.org/10.1038/nrn2298

Hovens IB, Schoemaker RG, van der Zee EA, Heineman E, Izaks GJ, van Leeuwen BL (2012) Thinking through postoperative cognitive dysfunction: how to bridge the gap between clinical and pre-clinical perspectives. Brain Behav Immun 26:1169–1179. https://doi.org/10.1016/j.bbi.2012.06.004

Hovens IB, Schoemaker RG, van der Zee EA, Absalom AR, Heineman E, van Leeuwen BL (2014) Postoperative cognitive dysfunction: involvement of neuroinflammation and neuronal functioning. Brain Behav Immun 38:202–210. https://doi.org/10.1016/j.bbi.2014.02.002

Hovens IB, van Leeuwen BL, Nyakas C, Heineman E, van der Zee EA, Schoemaker RG (2015) Postoperative cognitive dysfunction and microglial activation in associated brain regions in old rats. Neurobiol Learn Mem 118:74–79. https://doi.org/10.1016/j.nlm.2014.11.009

Hoy SM, Keating GM (2011) dexmedetomidine a review of its use for sedation in mechanically ventilated patients in an intensive care

setting and for procedural sedation. Drugs 71:1481–1501. https://doi.org/10.2165/11207190-000000000-00000

Hu J, Feng X, Valdearcos M, Lutrin D, Uchida Y, Koliwad SK, Maze M (2018) Interleukin-6 is both necessary and sufficient to produce perioperative neurocognitive disorder in mice. Br J Anaesth 120:537–545. https://doi.org/10.1016/j.bja.2017.11.096

Huang C, Irwin MG, Wong GTC, Chang RCC (2018) Evidence of the impact of systemic inflammation on neuroinflammation from a non-bacterial endotoxin animal model. J Neuroinflammation 15:147. https://doi.org/10.1186/s12974-018-1163-z

Hughes CG et al (2017) Surgery and anesthesia exposure is not a risk factor for cognitive impairment after major noncardiac surgery and critical illness. Ann Surg 265:1126–1133. https://doi.org/10.1097/SLA.0000000000001885

Jalal FY, Yang Y, Thompson JF, Roitbak T, Rosenberg GA (2015) Hypoxia-induced neuroinflammatory white-matter injury reduced by minocycline in SHR/SP. J Cereb Blood Flow Metab 35:1145–1153. https://doi.org/10.1038/jcbfm.2015.21

Jiang Y et al (2018) Upregulation of TREM2 ameliorates neuroinflammatory responses and improves cognitive deficits triggered by surgical trauma in Appswe/PS1dE9 Mice. Cell Physiol Biochem 46:1398–1411. https://doi.org/10.1159/000489155

Jyothi HJ et al (2015) Aging causes morphological alterations in astrocytes and microglia in human substantia nigra pars compacta. Neurobiol Aging 36:3321–3333. https://doi.org/10.1016/j.neurobiolaging.2015.08.024

Kakuta H, Zheng X, Oda H, Harada S, Sugimoto Y, Sasaki K, Tai A (2008) Cyclooxygenase-1-selective inhibitors are attractive candidates for analgesics that do not cause gastric damage. Design and in vitro/in vivo evaluation of a benzamide-type cyclooxygenase-1 selective inhibitor. J Med Chem 51:2400–2411. https://doi.org/10.1021/jm701191z

Kawano T, Eguchi S, Iwata H, Tamura T, Kumagai N, Yokoyama M (2015) Impact of preoperative environmental enrichment on prevention of development of cognitive impairment following abdominal surgery in a rat model. Anesthesiology 123:160–170. https://doi.org/10.1097/ALN.0000000000000697

Kohama SG, Goss JR, Finch CE, McNeill TH (1995) Increases of glial fibrillary acidic protein in the aging female mouse brain. Neurobiol Aging 16:59–67. https://doi.org/10.1016/0197-4580(95)80008-F

Kong F, Chen S, Cheng Y, Ma L, Lu H, Zhang H, Hu W (2013) Minocycline attenuates cognitive impairment induced by isoflurane anesthesia in aged rats. PLoS ONE 8:e61385. https://doi.org/10.1371/journal.pone.0061385

Kong FJ, Ma LL, Zhang HH, Zhou JQ (2015) Alpha 7 nicotinic acetylcholine receptor agonist GTS-21 mitigates isoflurane-induced cognitive impairment in aged rats. J Surg Res 194:255–261. https://doi.org/10.1016/j.jss.2014.09.043

Kubota K et al (2018) Age is the most significantly associated risk factor with the development of delirium in patients hospitalized for more than 5 days in surgical wards: retrospective cohort study. Ann Surg 267:874–877. https://doi.org/10.1097/SLA.0000000000002347

Lana D, Iovino L, Nosi D, Wenk GL, Giovannini MG (2016) The neuron-astrocyte-microglia triad involvement in neuroinflammaging mechanisms in the CA3 hippocampus of memory-impaired aged rats. Exp Gerontol 83:71–88. https://doi.org/10.1016/j.exger.2016.07.011

Le V et al (2016) Premedication with intravenous ibuprofen improves recovery characteristics and stress response in adults undergoing laparoscopic cholecystectomy: a randomized controlled trial. Pain Med. https://doi.org/10.1093/pm/pnv113

Li Q, Barres BA (2017) Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol. https://doi.org/10.1038/nri.2017.125

Li SY, Xia LX, Zhao YL, Yang L, Chen YL, Wang JT, Luo AL (2013) Minocycline mitigates isoflurane-induced cognitive impairment in aged rats. Brain Res 1496:84–93. https://doi.org/10.1016/j.brainres.2012.12.025

Li XM, Zhou MT, Wang XM, Ji MH, Zhou ZQ, Yang JJ (2014) Resveratrol pretreatment attenuates the isoflurane-induced cognitive impairment through its anti-inflammation and -apoptosis actions in aged mice. J Mol Neurosci 52:286–293. https://doi.org/10.1007/s12031-013-0141-2

Li Y et al (2016a) Deferoxamine regulates neuroinflammation and iron homeostasis in a mouse model of postoperative cognitive dysfunction. J Neuroinflammation 13:268. https://doi.org/10.1186/s12974-016-0740-2

Li Z et al (2016b) Surgery-induced hippocampal angiotensin II elevation causes blood–brain barrier disruption via MMP/TIMP in aged rats. Front Cell Neurosci 10:105. https://doi.org/10.3389/fncel.2016.00105

Liang Z et al (2017) Impact of aging immune system on neurodegeneration and potential immunotherapies. Prog Neurobiol 157:2–28. https://doi.org/10.1016/j.pneurobio.2017.07.006

Liddelow SA et al (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541:481–487. https://doi.org/10.1038/nature21029

Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013) The hallmarks of aging. Cell 153:1194–1217. https://doi.org/10.1016/j.cell.2013.05.039

Louveau A, Harris TH, Kipnis J (2015a) Revisiting the mechanisms of CNS immune privilege. Trends Immunol 36:569–577. https://doi.org/10.1016/j.it.2015.08.006

Louveau A et al (2015b) Structural and functional features of central nervous system lymphatic vessels. Nature 523:337–341. https://doi.org/10.1038/nature14432

Louveau A, Plog BA, Antila S, Alitalo K, Nedergaard M, Kipnis J (2017) Understanding the functions and relationships of the glymphatic system and meningeal lymphatics. J Clin Invest 127:3210–3219. https://doi.org/10.1172/JCI90603

Lv ZT, Huang JM, Zhang JM, Zhang JM, Guo JF, Chen AM (2016) Effect of ulinastatin in the treatment of postoperative cognitive dysfunction: review of current literature. Biomed Res Int 2016:2571080. https://doi.org/10.1155/2016/2571080

Ma Y, Cheng Q, Wang E, Li L, Zhang X (2015) Inhibiting tumor necrosis factor-alpha signaling attenuates postoperative cognitive dysfunction in aged rats. Mol Med Rep 12:3095–3100. https://doi.org/10.3892/mmr.2015.3744

Moller JT et al (1998) Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International study of post-operative cognitive dysfunction. Lancet 351:857–861

Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, Gravenstein JS (2008) Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 108:18–30. https://doi.org/10.1097/01.anes.0000296071.19434.1e

Montagne A et al (2015) Blood–brain barrier breakdown in the aging human hippocampus. Neuron 85:296–302. https://doi.org/10.1016/j.neuron.2014.12.032

Newfield P (2009) Postoperative cognitive dysfunction. Med Rep 1:14. https://doi.org/10.3410/m1-14

Ni P, Dong H, Wang Y, Zhou Q, Xu M, Qian Y, Sun J (2018) IL-17A contributes to perioperative neurocognitive disorders through blood–brain barrier disruption in aged mice. J Neuroinflammation 15:332. https://doi.org/10.1186/s12974-018-1374-3

Norden DM, Godbout JP (2013) Review: microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathol Appl Neurobiol 39:19–34. https://doi.org/10.1111/j.1365-2990.2012.01306.x

Paeschke N, von Haefen C, Endesfelder S, Sifringer M, Spies CD (2017) Dexmedetomidine prevents lipopolysaccharide-induced microRNA expression in the adult rat brain. Int J Mol Sci. https://doi.org/10.3390/ijms18091830

Pan K, Li X, Chen Y, Zhu D, Li Y, Tao G, Zuo Z (2016) Deferoxamine pre-treatment protects against postoperative cognitive dysfunction of aged rats by depressing microglial activation via ameliorating iron accumulation in hippocampus. Neuropharmacology 111:180–194. https://doi.org/10.1016/j.neuropharm.2016.09.004

Peng M, Wang YL, Wang FF, Chen C, Wang CY (2012) The cyclooxygenase-2 inhibitor parecoxib inhibits surgery-induced proinflammatory cytokine expression in the hippocampus in aged rats. J Surg Res 178:e1–8. https://doi.org/10.1016/j.jss.2012.08.030

Perea G, Navarrete M, Araque A (2009) Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci 32:421–431. https://doi.org/10.1016/j.tins.2009.05.001

Pizza V, Agresta A, D'Acunto CW, Festa M, Capasso A (2011) Neuroinflamm-aging and neurodegenerative diseases: an overview. CNS Neurol Disord 10:621–634

Qiu LL et al (2016) NADPH oxidase 2-derived reactive oxygen species in the hippocampus might contribute to microglial activation in postoperative cognitive dysfunction in aged mice. Brain Behav Immun 51:109–118. https://doi.org/10.1016/j.bbi.2015.08.002

Rawji KS, Mishra MK, Michaels NJ, Rivest S, Stys PK, Yong VW (2016) Immunosenescence of microglia and macrophages: impact on the ageing central nervous system. Brain 139:653–661. https://doi.org/10.1093/brain/awv395

Rosczyk HA, Sparkman NL, Johnson RW (2008) Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol 43:840–846. https://doi.org/10.1016/j.exger.2008.06.004

Salter MW, Stevens B (2017) Microglia emerge as central players in brain disease. Nat Med 23:1018–1027. https://doi.org/10.1038/nm.4397

Sampson TR et al (2016) Gut microbiota regulate motor deficits and neuroinflammation in a model of parkinson's disease. Cell 167(1469–1480):e1412. https://doi.org/10.1016/j.cell.2016.11.018

Schloesser RJ, Lehmann M, Martinowich K, Manji HK, Herkenham M (2010) Environmental enrichment requires adult neurogenesis to facilitate the recovery from psychosocial stress. Mol Psychiatry 15:1152–1163. https://doi.org/10.1038/mp.2010.34

Schuitemaker A et al (2012) Microglial activation in healthy aging. Neurobiol Aging 33:1067–1072. https://doi.org/10.1016/j.neurobiolaging.2010.09.016

Schwartz M, Kipnis J, Rivest S, Prat A (2013) How do immune cells support and shape the brain in health, disease, and aging? J Neurosci 33:17587–17596. https://doi.org/10.1523/JNEUROSCI.3241-13.2013

Skvarc DR et al (2018) Post-operative cognitive dysfunction: an exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev 84:116–133. https://doi.org/10.1016/j.neubiorev.2017.11.011

Sochocka M, Diniz BS, Leszek J (2017) Inflammatory response in the CNS: friend or foe? Mol Neurobiol 54:8071–8089. https://doi.org/10.1007/s12035-016-0297-1

Sofroniew MV (2014) Astrogliosis. Cold Spring Harb Perspect Biol 7:a020420. https://doi.org/10.1101/cshperspect.a020420

Sofroniew MV, Vinters HV (2010) Astrocytes: biology and pathology. Acta Neuropathol 119:7–35. https://doi.org/10.1007/s00401-009-0619-8

Soreq L et al (2017) Major shifts in glial regional identity are a transcriptional hallmark of human brain aging. Cell Rep 18:557–570. https://doi.org/10.1016/j.celrep.2016.12.011

Sprung J et al (2017) Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth 119:316–323. https://doi.org/10.1093/bja/aex130

Steinmetz J, Christensen KB, Lund T, Lohse N, Rasmussen LS, Group I (2009) Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 110:548–555. https://doi.org/10.1097/ALN.0b013e318195b569

Stogsdill JA et al (2017) Astrocytic neuroligins control astrocyte morphogenesis and synaptogenesis. Nature 551:192–197. https://doi.org/10.1038/nature24638

Stollings LM, Jia LJ, Tang P, Dou H, Lu B, Xu Y (2016) Immune modulation by volatile anesthetics. Anesthesiology 125:399–411. https://doi.org/10.1097/ALN.0000000000001195

Su X et al (2016) Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet 388:1893–1902. https://doi.org/10.1016/S0140-6736(16)30580-3

Sun L, Dong R, Xu X, Yang X, Peng M (2017) Activation of cannabinoid receptor type 2 attenuates surgery-induced cognitive impairment in mice through anti-inflammatory activity. J Neuroinflammation 14:138. https://doi.org/10.1186/s12974-017-0913-7

Tchkonia T, Kirkland JL (2018) Aging, cell senescence, and chronic disease: emerging therapeutic strategies. JAMA. https://doi.org/10.1001/jama.2018.12440

Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M (2010) Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. Proc Natl Acad Sci USA 107:20518–20522. https://doi.org/10.1073/pnas.1014557107

Terrando N et al (2011) Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol 70:986–995. https://doi.org/10.1002/ana.22664

Terrando N, Eriksson LI, Eckenhoff RG (2015a) Perioperative neurotoxicity in the elderly: summary of the 4th International Workshop. Anesth Analg 120:649–652. https://doi.org/10.1213/ANE.0000000000000624

Terrando N et al (2015b) Stimulation of the alpha7 nicotinic acetylcholine receptor protects against neuroinflammation after tibia fracture and endotoxemia in mice. Mol Med (Cambridge, Mass) 20:667–675. https://doi.org/10.2119/molmed.2014.00143

Terrando N et al (2016) Systemic HMGB1 o. Front Immunol 7:441. https://doi.org/10.3389/fimmu.2016.00441

Thion MS et al (2018) Microbiome influences prenatal and adult microglia in a sex-specific manner. Cell 172(500–516):e516. https://doi.org/10.1016/j.cell.2017.11.042

Trivino-Paredes J, Patten AR, Gil-Mohapel J, Christie BR (2016) The effects of hormones and physical exercise on hippocampal structural plasticity. Front Neuroendocrinol 41:23–43. https://doi.org/10.1016/j.yfrne.2016.03.001

Vacas S, Degos V, Feng X, Maze M (2013) The neuroinflammatory response of postoperative cognitive decline. Br Med Bull 106:161–178. https://doi.org/10.1093/bmb/ldt006

Vacas S, Degos V, Tracey KJ, Maze M (2014) High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. Anesthesiology 120:1160–1167. https://doi.org/10.1097/ALN.0000000000000045

Vacas S, Degos V, Maze M (2017) Fragmented sleep enhances postoperative neuroinflammation but not cognitive dysfunction. Anesth Analg 124:270–276. https://doi.org/10.1213/ANE.0000000000001675

Vaiserman AM, Koliada AK, Marotta F (2017) Gut microbiota: a player in aging and a target for anti-aging intervention. Ageing Res Rev 35:36–45. https://doi.org/10.1016/j.arr.2017.01.001

van de Haar HJ, Burgmans S, Hofman PA, Verhey FR, Jansen JF, Backes WH (2015) Blood–brain barrier impairment in dementia:

current and future in vivo assessments. Neurosci Biobehav Rev 49:71–81. https://doi.org/10.1016/j.neubiorev.2014.11.022

Vasto S et al (2007) Inflammatory networks in ageing, age-related diseases and longevity. Mech Ageing Dev 128:83–91. https://doi.org/10.1016/j.mad.2006.11.015

Vincent JA, Mohr S (2007) Inhibition of caspase-1/interleukin-1β signaling prevents degeneration of retinal capillaries in diabetes and galactosemia. Diabetes 56:224–230. https://doi.org/10.2337/db06-0427

Wan Y, Xu J, Ma D, Zeng Y, Cibelli M, Maze M (2007) Postoperative impairment of cognitive function in rats: a possible role for cytokine-mediated inflammation in the hippocampus. Anesthesiology 106:436–443

Wan Y et al (2010) Cognitive decline following major surgery is associated with gliosis, beta-amyloid accumulation, and tau phosphorylation in old mice. Crit Care Med 38:2190–2198. https://doi.org/10.1097/CCM.0b013e3181f17bcb

Wang B et al (2017a) Blood–brain barrier disruption leads to postoperative cognitive dysfunction. Curr Neurovasc Res 14:359–367. https://doi.org/10.2174/1567202614666171009105825

Wang KY, Yang QY, Tang P, Li HX, Zhao HW, Ren XB (2017b) Effects of ulinastatin on early postoperative cognitive function after one-lung ventilation surgery in elderly patients receiving neoadjuvant chemotherapy. Metab Brain Dis 32:427–435. https://doi.org/10.1007/s11011-016-9926-7

Wang Z, Meng S, Cao L, Chen Y, Zuo Z, Peng S (2018) Critical role of NLRP3-caspase-1 pathway in age-dependent isoflurane-induced microglial inflammatory response and cognitive impairment. J Neuroinflammation 15:109. https://doi.org/10.1186/s12974-018-1137-1

Wu X et al (2017) Curcumin attenuates surgery-induced cognitive dysfunction in aged mice. Metab Brain Dis 32:789–798. https://doi.org/10.1007/s11011-017-9970-y

Xiong C, Liu J, Lin D, Zhang J, Terrando N, Wu A (2018) Complement activation contributes to perioperative neurocognitive disorders in mice. J Neuroinflammation 15:254. https://doi.org/10.1186/s12974-018-1292-4

Xu Z et al (2014) Age-dependent postoperative cognitive impairment and Alzheimer-related neuropathology in mice. Sci Rep 4:3766. https://doi.org/10.1038/srep03766

Xu J, Dong H, Qian Q, Zhang X, Wang Y, Jin W, Qian Y (2017) Astrocyte-derived CCL2 participates in surgery-induced cognitive dysfunction and neuroinflammation via evoking microglia activation. Behav Brain Res 332:145–153. https://doi.org/10.1016/j.bbr.2017.05.066

Yang S et al (2017) Anesthesia and surgery impair blood–brain barrier and cognitive function in mice. Front Immunol 8:902. https://doi.org/10.3389/fimmu.2017.00902

Ye JS, Chen L, Lu YY, Lei SQ, Peng M, Xia ZY (2018) SIRT3 activator honokiol ameliorates surgery/anesthesia-induced cognitive decline in mice through anti-oxidative stress and anti-inflammatory in hippocampus. CNS Neurosci Ther. https://doi.org/10.1111/cns.13053

Yin JA et al (2017) Genetic variation in glia-neuron signalling modulates ageing rate. Nature 551:198–203. https://doi.org/10.1038/nature24463

Yrjanheikki J, Tikka T, Keinanen R, Goldsteins G, Chan PH, Koistinaho J (1999) A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc Natl Acad Sci USA 96:13496–13500. https://doi.org/10.1073/pnas.96.23.13496

Zhan G et al (2018) Abnormal gut microbiota composition contributes to cognitive dysfunction in SAMP8 mice. Aging 10:1257–1267. https://doi.org/10.18632/aging.101464

Zhang X, Yao H, Qian Q, Li N, Jin W, Qian Y (2016) Cerebral mast cells participate in postoperative cognitive dysfunction by promoting astrocyte activation. Cell Physiol Biochem 40:104–116. https://doi.org/10.1159/000452528

Zhang DF et al (2018) Impact of dexmedetomidine on long-term outcomes after noncardiac surgery in elderly: 3-year follow-up of a randomized controlled trial. Ann Surg. https://doi.org/10.1097/sla.0000000000002801

Zhao Y et al (2016) Neuroinflammation induced by surgery does not impair the reference memory of young adult mice. Mediat Inflamm 2016:3271579. https://doi.org/10.1155/2016/3271579

Zhao WX et al (2017) Acetaminophen attenuates lipopolysaccharide-induced cognitive impairment through antioxidant activity. J Neuroinflammation 14:17. https://doi.org/10.1186/s12974-016-0781-6

Zheng B, Lai R, Li J, Zuo Z (2017) Critical role of P2X7 receptors in the neuroinflammation and cognitive dysfunction after surgery. Brain Behav Immun 61:365–374. https://doi.org/10.1016/j.bbi.2017.01.005

Zhu YJ, Peng K, Meng XW, Ji FH (2016a) Attenuation of neuroinflammation by dexmedetomidine is associated with activation of a cholinergic anti-inflammatory pathway in a rat tibial fracture model. Brain Res 1644:1–8. https://doi.org/10.1016/j.brainres.2016.04.074

Zhu YZ, Yao R, Zhang Z, Xu H, Wang LW (2016b) Parecoxib prevents early postoperative cognitive dysfunction in elderly patients undergoing total knee arthroplasty: a double-blind, randomized clinical consort study. Medicine 95:e4082. https://doi.org/10.1097/md.0000000000004082

Zhu H, Liu W, Fang H (2018) Inflammation caused by peripheral immune cells across into injured mouse blood brain barrier can worsen postoperative cognitive dysfunction induced by isoflurane. BMC Cell Biol 19:23. https://doi.org/10.1186/s12860-018-0172-1

Zlokovic BV (2008) The blood–brain barrier in health and chronic neurodegenerative disorders. Neuron 57:178–201. https://doi.org/10.1016/j.neuron.2008.01.003