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Chapter 7

Postoperative Cognitive Dysfunction: Preclinical Highlights and Perspectives on Preventive Strategies

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Abstract

One of the common complications associated with anaesthesia and surgery in geriatric patients is the postoperative cognitive dysfunction (POCD). This cognitive impairment affects the long-term prognosis and has been shown to be associated with long-term disability, higher health care costs, and even increased mortality. On the other hand, clinical research on POCD is in its infancy, the condition has not been clarified, and since no strategy for management is currently available, it is imperative to develop specific methods for prevention and management. Although its pathogenesis involves various factors, accumulating evidence suggests that surgery elicits an inflammatory response in the hippocampus, a brain area closely related to cognitive function, playing a key role in the development of POCD. Several studies suggest that age-related phenotypic change of microglia is associated with pathogenic neuroinflammation, and more importantly it may be modifiable. In this chapter, we discuss the current overview and preclinical highlights regarding POCD. We further discuss some perspectives on preventive strategies for POCD, based on the findings of our preclinical research and the available literature.

Keywords: POCD, neuroinflammation, microglia

1. Introduction

Sixty years ago, an article entitled *Adverse cerebral effects of anaesthesia on old people* by Dr. Bedfor was published in which he reported for the first time that general anaesthesia and surgery led to cognitive dysfunction in elderly patients [1]. This decline, known as postoperative cognitive dysfunction (POCD), typically persists for several weeks, sometimes a year, but in some people is permanent. Since then, the number of publications assessing POCD has been growing year by year, reflecting the increasing importance and the still remaining controversies over this condition [2].

One of the greatest achievements of modern medicine is the increase in life expectancy; however, as a consequence the world population is today ageing fast, with over 12.3% of the total being over 60 years old [3]. Moreover, life expectancy increased by 5 years between 2000 and 2015, the fastest growth since the 1960s [4]. Though it is one of our greatest achievements, it also poses big challenges as the ageing process is associated with biological and cognitive degeneration [5]. Recent advances in surgical, anaesthetic management and intensive care techniques are associated with a growing number of elderly people undergoing surgical procedures [6]. Consequently, complications associated with geriatric surgery, such as POCD, will become an increasingly common worldwide problem [7, 8]. Furthermore, POCD has been shown to be associated with long-term disability and higher health care costs. In addition, three-month POCD has been statistically associated with increased mortality [9].

POCD is difficult to define; in general it refers to a deterioration in cognition that occurs in the time period after surgery. To truly diagnose POCD, it is necessary to have tested the patient preoperatively (baseline) and determined how much of a decline occurred after surgery. As can be expected, in normal clinical contexts, patients do not usually undergo neuropsychological testing pre- and post-surgery [2, 10]. In consequence, there is a lack of accurate data and even the exact incidence of this condition is unknown [10]. Besides, behavioral responses to cognitive tests not only vary considerably in aged individuals compared with younger individuals, but also an enormous variability of cognitive decline exists across individuals [6, 11]. Additionally, the changes produced by the effects of ageing on cognitive function vary substantially through the different cognitive domains [11]. Likewise, different cognitive domains must be evaluated by specific tests [2]. Hence in order to diagnose and characterize POCD cases, it becomes necessary to carry out neuropsychological tests that assess different domains involved in cognitive function such as learning and memory, attention, psychomotor function and flexibility cognition [2, 10]. In addition, POCD is sometimes characterized by slight declines in cognitive function, making it essential that these tests should be sensitive enough to allow an accurate diagnosis based on the results of pre-and postoperative tests [10]. As a consequence, incidence rates reported may vary considerably according to the cognitive domains explored by different tests and timing [12].

POCD was initially associated with cardiac surgery and indeed was recognized as the most common complication in this intervention, presenting a high incidence [13, 14], although the incidence values vary considerably between different reports, ranging from approximately 30% to 80% at the time of discharge, 10–60% after 3–6 months and 20–60% after 6 months to 1 year [12–20]. This fact may be related to microembolic events that may cause focal cerebral infarcts during the use of the cardiopulmonary bypass pump [12, 21–24].

In recent times, in correlation with the continuingly increasing number of patients undergoing geriatric surgery, the interest in POCD has expanded to noncardiac surgery as well. So far, the major study assessing this condition was carried out by the International Study of Postoperative Cognitive Dysfunction and included 1218 patients older than 60 years old undergoing elective, noncardiac surgery [7]. Neuropsychological tests were administered

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before surgery and at 7 days and 3 months after intervention. This study reported a POCD incidence of 25% 1 week after surgery and 10% after 3 months. Additionally, the probability of POCD incidence in patients aged 70 and over at 3 months (14%) was two times higher than those aged 60 to 69 (7%). Hovens and collaborators [25] reported that the cognitive domains affected by cardiac surgery compared with noncardiac surgery seem to be different. While abdominal surgery affects hippocampal neuronal functioning and in consequence spatial memory, cardiac surgery seems to cause a more general change in inflammation and neuronal function [25].

Furthermore, there appears to exist an association between postoperative pain and cognitive impairment, exerting an influence over the patients' performance on certain cognitive tests [26–28]. Apart from the effect of the pain, the influence of postoperative analgesics should not be ruled out. In fact, successful postoperative pain management may be important in preventing POCD in elderly patients [35]. Additionally, cognitive impairment in elderly patients may also be influenced by stress produced by the hospitalization itself, the postoperative fatigue state, the unfamiliar environment and sleep deprivation [12, 28, 29].

The contribution of the anaesthesia to the development of POCD seems to be subject to discrepancies. When Silbert and colleagues [30] assessed general anaesthesia compared with spinal anaesthesia, no significant difference in the rates of POCD was found. In agreement with this, a meta-analysis carried on by Guay [31] did not find differences between general anaesthesia and regional anaesthesia with spontaneous breathing and sedation only in the development of permanent POCD after noncardiac surgery. Otherwise, another meta-analysis concluded that general anaesthesia, compared to other types of anaesthesia, may increase the risk of developing POCD [32]. This findings are supported by preclinical studies, which suggest that isoflurane anaesthesia administered at clinically relevant doses causes long-term cognitive impairment in unoperated animals [33–35]. However, other studies point towards an enhancement of the cognitive functions after anaesthesia inhalation [36–38].

Although major surgery is frequently associated with the development of POCD, minor surgery proved to decrease the cognitive function in the first postoperative week in elderly patients [39]. Moreover, independently from the nature of the surgical procedure, the only consistent risk factor that has been identified for POCD is advanced age [7, 9, 15, 39–41]. Apart from increasing age as a risk factor for POCD, other factors that can be enumerated are lower level of education, a history of previous cerebral vascular accident, a history of alcohol dependence, preoperative history of post-traumatic stress disorder, poor cognitive health, preceding development of POCD, respiratory complications, infectious complications and a second operation [9, 12, 41–43].

2. Mechanisms of POCD

One of the most challenging problems connected with POCD is the lack of evidence-based preventative strategies. This is due to the fact that the mechanisms that cause POCD in

elderly patients are largely unknown. In fact, surgery induces peripheral immune challenges, leading to an exaggerated neuroinflammatory response. More recently, several studies have demonstrated that neuroinflammation in the hippocampus is most likely to be involved in the pathogenesis of POCD [35, 44–51]. Neuroinflammation is a complex response to brain injury characterized by maladaptive microglial activation mainly involving the activation of glia and increased levels of pro-inflammatory cytokines, including interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) [52–54]. As the primary source for pro-inflammatory cytokines, microglia are implicated as pivotal mediators of neuroinflammation. In particular, the hippocampus is known to be a region important to cognition and highly vulnerable to ageing. Pro-inflammatory cytokines TNF-α and IL-1β released from microglia within the hippocampus are reported to inhibit the long-term potentiation that is important in the formation of memory, as well as inducing apoptosis, and thus play a pathogenic role in cognitive disorders in neurodegenerative diseases [48, 52–58]. Based on these findings, it can be hypothesized that age-related microglial priming in the hippocampus, and subsequent overproduction of inflammatory cytokines, plays a critical role in the development of POCD in the elderly population. Therefore, it becomes necessary to understand the roles of neuroinflammation in the pathogenesis of POCD and its potential as a therapeutic target.

Preclinical evidence has shown that microglia in a normal-aged brain are shifted towards the inflammatory phenotype (**Figure 1**). This age-related phenotype change is consistent with the microglial priming, implying that age-related microglia priming could make elderly surgical patients more susceptible to the development of POCD. Neurogenic neuroinflammation is the inflammatory reaction in the central nervous system in response to neuronal activity [59]. Peripheral immune challenges, such as surgical trauma, may lead neurogenic neuroinflammation to become maladaptive [60]. It has been postulated that the inflammatory response may be transmitted through humoral and neural pathways, leading to neuroinflammation. Parabiotic experiments in rat models have revealed that the neural pathway may play a dominant role in the development of neuroinflammation after abdominal surgery [60]. These findings seem to confirm the neurogenic neuroinflammatory origin of POCD in aged rats. Though rodents are useful in providing hypothetical models for understanding some of the memory deficits seen in human POCD, it still remains unclear how much can be extrapolated to simulate the neuroinflammatory mechanisms involved in human POCD [2].

While several studies have concentrated on protein regulating inflammation (cytokines), recent evidence points to a critical role of microRNAs (miRNAs) in controlling the inflammatory process [61–64]. A subset of miRNAs notably affects both immune and neuronal functions in particular in the central nervous system. It has been hypothesized that miRNAs regulate neuro-immune functions through alterations of neuron-glia and/or brain-to-body signalling [65]. Moreover, miR-572 has been implicated in the development and restoration of POCD and identified as a possible biological marker for early diagnosis of POCD [61]. In fact, modulating miRNAs using agonist or antagonist miRNAs is a promising approach to treating human neuroinflammatory disorders including POCD.

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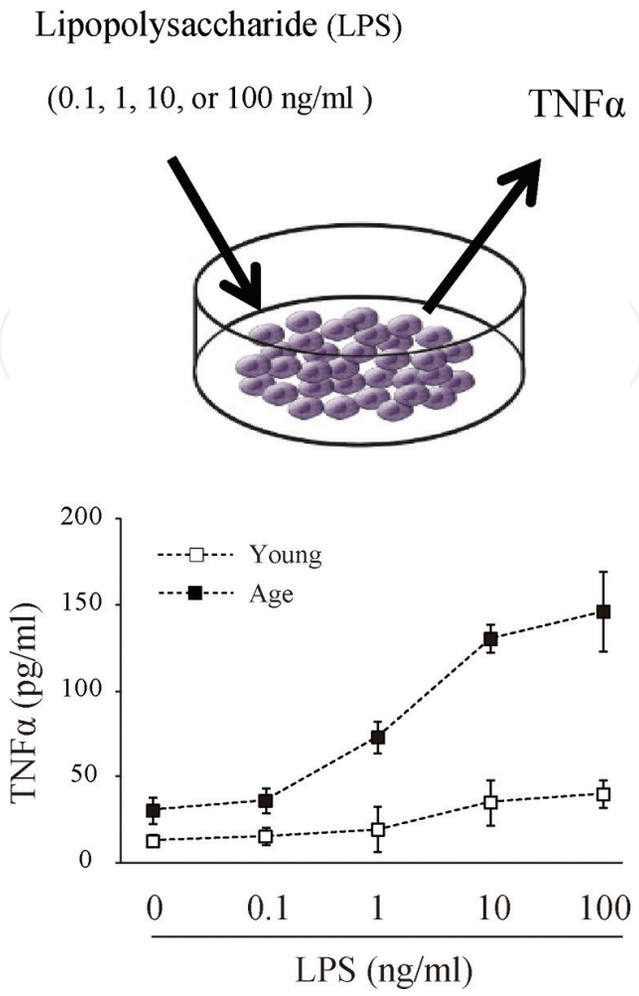

Figure 1. Microglial priming. Effects of ex vivo stimulation with lipopolysaccharide (LPS) on the cultured microglia were shown. Hippocampal microglia were isolated from either young or aged rats. Primary microglia were stimulated with 0.1, 1, 10 and 100 ng/ml or media alone, and levels of TNF-α were determined from supernatants collected 24 h later. The LPS-induced increase in TNF-α was greater in the microglia of aged rats than young. These results indicate that normal ageing may prime microglia for an exaggerated responsiveness to pro-inflammatory stimuli.

3. Treatment and prevention

Notwithstanding the fact that POCD is a common complication for geriatric patients, currently there is not any available st ment after general anaesthesia [66]. Additionally, due to the challenging nature of POCD, examples of randomized controlled studies assessing possible intervention for treating or improving POCD are scarce [2]. However, this can be addressed by studies assessing the effects of drugs on cognitive impairment after general anaesthesia. Aminophylline reduced the time necessary for postoperative cognitive recovery from sevoflurane anaesthesia, improving the ventilatory elimination of sevoflurane [67]. Meanwhile, low-dose haloperidol prophylactic treatment did not prove effective in decreasing the incidence of postoperative delirium but had a positive effect on the severity and duration [68]. A pilot, phase 2a study to evaluate the feasibility, safety and efficacy of donepezil in preventing

postoperative delirium did not find significant changes in the incidence of delirium or in the days patients stayed in the hospital, although it did not rule out possible benefits [69]. In agreement with these results, Doraiswamy and collaborators [70] evaluated the effect of donepezil in treating patients with cognitive decline following coronary artery bypass graft surgery, reporting that donepezil did not improve composite cognitive performance but had enhancing effects on some aspects of memory. Meanwhile, the use of gabapentin in the treatment of postoperative pain reduced the occurrence of postoperative delirium [71].

Therefore, the lack of an effective treatment for POCD highlights the importance of the prevention. Over the past years, research efforts have been directed to identifying new strategies for preventing POCD [2]. While lidocaine administered during and after cardiac surgery failed to reduce POCD incidence, some protective effects of lower-dose lidocaine in nondiabetic subjects were found [72]. Moreover, due the anti-inflammatory action of ketamine, POCD incidence was reduced one week after cardiac surgery [73]. Meanwhile, intraoperatively intravenous administration of magnesium in cardiac surgery did not have any preventive effect over POCD [74]. Furthermore, administration of a post-cardiac surgery high dose of dexamethasone failed to reduce the risk of POCD [75], while in another study, a higher dose of dexamethasone actually increased the incidence of POCD in the early postoperative period after microvascular decompression under general anaesthesia [76]. Furthermore, resveratrol showed anti-neuroinflammation and anti-apoptosis effects attenuating the hippocampus-dependent cognitive impairment induced by isoflurane in aged mice [77]. Also, ondansetron administered postoperatively appears to have analgesic and protective effects, additionally seeming to improve the cognitive function in patients undergoing surgery under general anaesthesia [78]. When the effects of postoperative analgesia with ketoprofen on cognitive functions were investigated in aged animals, the results suggested that ketoprofen can prevent the development of surgery-associated memory deficits via its pain-relieving effects [79]. Chronic pretreatment with low doses of candesartan may elicit blood pressure-independent neuroprotective effects in POCD by decreasing hippocampal blood-brain barrier permeability and promoting resolution of neuroinflammation [47]. Further, dexmedetomidine provided neurocognitive protection, attenuating isoflurane-induced injury in rats developing brain [80]. Atorvastatin preserved the hippocampal-dependent fear response and also protected spatial memory on day seven after surgery in a mouse model of postoperative cognitive decline [81]. Aspirin-triggered resolvin D1 prevented neuronal dysfunction and cognitive decline after peripheral orthopaedic surgery in the mouse model [82].

There is considerable evidence that cognitive interventions, such as physical activity and cognitive activity, have positive effects on age-related cognitive changes as well as early-stage dementia in humans [83–89]. In addition, animal models mimicking these interventions, in which rodents were exposed to voluntary wheel running and an enriched environment, showed improvement in cognitive performance (**Figure 2**) [48, 90]. Although the mechanism of these benefits has been debated, both interventions are reported to have common positive effects on microglial number, proliferation and phenotype in the brain. In fact, preoperative cognitive intervention, a combination of physical activity and cognitive activity, has been shown to prevent the development of POCD via restoration of the pro-inflammatory phenotype in aged microglia [48]. In addition, evidence suggests

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that an enriched environment attenuated the surgery effects in reduction of brain-derived neurotrophic factor (BDNF) expression and neurogenesis in the hippocampus [90]. Recent time-course analysis using a rat abdominal surgery model revealed that hippocampal neuroinflammation and related microglial activation were found at 7 days after surgery, which resolved to normal levels by 14 days after surgery [48]. Therefore, the effects of preoperative cognitive intervention may persist long enough to encompass the critical period of POCD development [48].

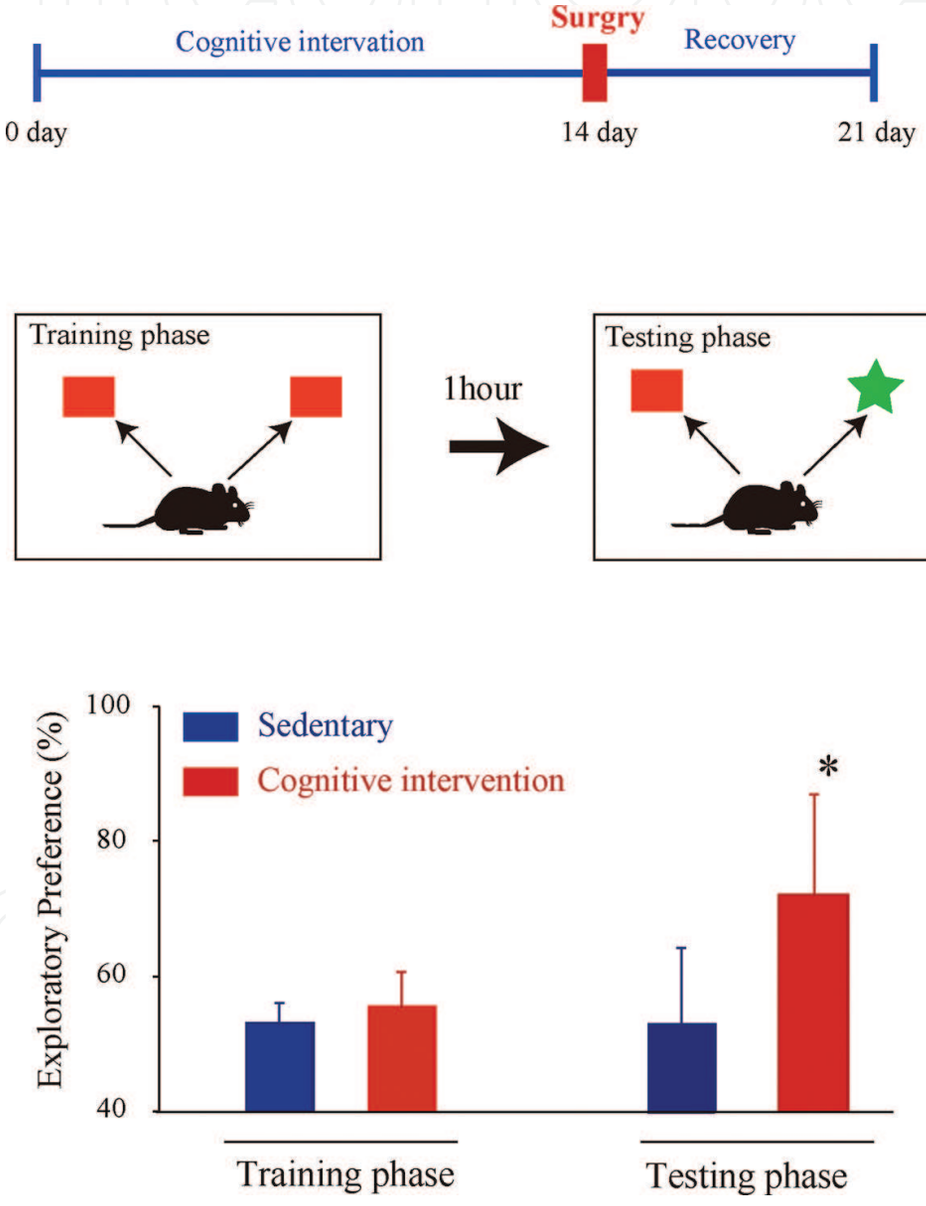

Figure 2. Effects of preoperative cognitive intervention on cognitive function assessed by novel object recognition test in aged rats. All rats were exposed to preoperative cognitive intervention or sedentary condition for 14 days following surgery (laparotomy and small intestinal manipulation) or non-surgery and allowed 7 days of recovery. Seven days after surgery, the effects of cognitive intervention on hippocampal-mediated working memory were assessed by a novel object recognition task. The sedentary rats in the aged group exhibited significantly impaired novel object recognition performance as shown by the similar amount of time spent in exploring the two objects. However, such impairment was not observed in the preoperative cognitive intervention group.

4. Concluding remarks

POCD is increasingly recognized as one of the common complications in geriatric patients despite the lack of strategy for prevention and management. Due to these limitations, preoperative management should be focused on promoting an early recognition of the patients at risk, and preventative measures should be taken from a multimodal approach comprising collaboration between the anaesthesiologist, surgeon, geriatricians and inclusion of family in the postoperative care plan in order to improve overall recovery and avoid long-term sequelae of POCD [2, 6, 10, 66]. Furthermore, it is recommended that patients at high risk for POCD should get preoperative discussion of this issue, allowing patients to make cognitively demanding decisions before surgery [2]. In addition, in line with the positive effects of cognitive interventions in both human and animal models, "pre-surgical rehabilitation" must be encouraged when possible in order to minimize the risk of POCD occurrence and its effects on overall recovery after surgery [2]. Moreover, promising new approaches such as the utilization of the relationship between neuroinflammation and miRNA expression should not be overlooked, in order to understand and discover new treatments. Deregulation of certain miRNAs may be associated with POCD development.

While both cardiac surgery and noncardiac surgery have been associated with POCD, the effects of each seem to affect different cognitive domains and in consequence may originate from different causes or mechanisms [25]. Moreover, the difficulty extrapolating the knowledge gathered through preclinical studies and animal models to human cases and the translation of these findings into therapeutic treatment for POCD points to the need for further work is needed. So far, the surgery-induced neuroinflammation processes including the microglial activation pathways seem to be the most promising therapeutic targets in the management of POCD.

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