

Impact on the brain of the inflammatory response to surgery

Sarah Saxena^{1,2}, Mervyn Maze¹

Available online:

1. Center for Cerebrovascular Research, Department of Anesthesia and Perioperative Care, UCSF
2. Department of anesthesia, Université Libre de Bruxelles, Belgium

Correspondence:

Mervyn Maze, Zuckerberg San Francisco General, 1001, Potrero avenue, building 10 Room 1206, 94110-3518, San Francisco, CA, United States.
mervyn.maze@ucsf.edu

In this issue

Editorial: Post-operative cognitive disorders: a new model for perioperative medicine.

A. Jacquens, et al.

Anesthesia and the risk of dementia in elderly.

J. Steinmetz, et al. (Denmark)

Postoperative Delirium.

K.F. Rengel, et al. (USA)

Tools to screen and measure cognitive impairment after surgery and anesthesia.

S. Vide, et al. (Spain, Portugal, USA)

Impact on the brain of the inflammatory response to surgery.

S. Saxena, et al. (Belgium, USA)

Summary

The brain is both the orchestrator as well as the target of the innate immune system's response to the aseptic trauma of surgery. When trauma-induced inflammation is not appropriately regulated persistent neuro-inflammation interferes with the synaptic plasticity that underlies the learning and memory aspects of cognition. The complications that ensue, include postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) at two poles of a constellation that is now termed perioperative neurocognitive disorders. While the relationship of acute POD to the more indolent POCD is not completely understood both can be further complicated by earlier-onset of dementia and higher mortality. How and why these disorders occur is the focus of this report. The innate immune system response to peripheral trauma signals to the brain through a regulated cascade of cellular and molecular actors producing a teleological defense mechanism, "sickness behavior," to curtail further injury and initiate repair. Sickness behavior, including disordered cognition, is terminated by neural and humoral pathways that restore homeostasis and launch the organism on a path to good health. With so many "moving parts" the innate immune system is vulnerable in clinical settings that include advanced age and lifestyle-induced diseases such as "unhealthy" obesity and the inevitable insulin resistance. Under these conditions, inflammation may become exaggerated and long-lived. Consideration is provided how to identify the high-risk surgical patient and both pharmacological (including biological compounds) and non-pharmacological strategies to customize care.

Introduction

Postoperative cognitive decline (PCD), a major surgical complication, is defined by deterioration in cognitive performance using a battery of neuropsychological tests that are administered before and after surgery [1]. According to the Center for Disease Control more than 40% of surgical procedures in the US are performed on patients aged ≥ 65 [2]. This age group most frequently

develops both the indolent postoperative cognitive dysfunction (POCD) as well as the acute postoperative delirium (POD). Postoperative delirium (POD) is an acute event lasting hours to days after surgery. It is a short-lived condition defined by several easily-established criteria in the DSM V. POD occurs in 15 to 53% of older surgical patients and POCD incidence ranges from 8.9% to 46.1% [2]. Both POD and POCD are associated with higher mortality, increased incidence of postoperative complications, longer duration of hospital stay, greater utilization of societal assistance and earlier retirement.

A new terminology has been advocated for these cognitive complications of surgery to align with the psychiatric lexicon in order to increase both awareness and precision. "Perioperative neurocognitive disorders" is the new overarching term for cognitive impairment or change identified between the preoperative or postoperative periods [3].

Delayed neurocognitive recovery can occur up to 30 days after surgery and a postoperative neurocognitive disorder (for example, memory loss) can develop up to 12 months after intervention. Neurocognitive disorders have a major impact on the patients' daily quality of life. The link between perioperative neurocognitive disorders and dementia is still unclear although both dementia and increased mortality may eventuate [4-6].

An organism launches a "sickness behavior" response following infection or trauma. Sickness behavior, a teleological defense mechanism, refers to the coordinated set of behavioral changes (elevated body temperature, increased sleep, decreased appetite) that develop in sick individuals during the course of an infection or trauma. Although helpful in an acute phase, as it promotes the survival of the organism, in a chronic state sickness behavior can lead to a reduced quality of life, both mentally and physically [5,7,8].

Our understanding of the underlying mechanisms for the development of postoperative neurocognitive disorders will enable identification of possible targets for interventions. In this report, we focus on how changes are induced in the central nervous system following peripheral surgery.

Overview of innate immune response to peripheral trauma

The innate immune system is a generic component of the organism's response to infection or tissue damage. Activation of this system starts the inflammatory process, which can eventually lead to postoperative cognitive decline [9-11]. The following is a brief overview of the cellular, molecular and system-wide processes that are involved (*figure 1*).

Cell trauma releases molecules known as damage associated molecular patterns (DAMPs) [9,12-14]. The DAMP, high mobility group box-1 (HMGB1), is passively released from cells damaged by aseptic trauma and targets circulating bone marrow-derived monocytes (BM-DMs) [15-18]. HMGB-1 can bind to pattern-recognition receptors including Toll-like receptors as well as

the receptor for advanced glycation end-product both of which signal to activate NF- κ B, a transcription factor that leads to upregulation of the synthesis and release of pro-inflammatory cytokines [19]. In the cytoplasm, NF- κ B is normally bound and inhibited by I κ B. Once HMGB-1 signaling begins, I κ B becomes phosphorylated and releases NF- κ B which translocates into the nucleus. Within the nucleus the NF- κ B dimer up-regulates genes for the pro-inflammatory cytokines including TNF- α , IL-1 β , and IL-6. These cytokines are released into the circulation and disrupt the integrity of the blood brain barrier (BBB) [11,15,20-23].

BM-DMs penetrate into the brain through the disrupted BBB and are attracted by the chemokine monocyte chemo-attractant protein 1 (MCP-1); BM-DMs express the surface marker, chemokine receptor type 2 (CCR2), a receptor for MCP-1 [24]. After the BM-DM enters the brain parenchyma, the quiescent microglia become activated, possibly through release of cytokines by CCR2-expressing monocytes [25].

Peripherally-released cytokines act on the afferent arm of a vagal reflex arc. The efferent arm of the vagal reflex signals to choline acetyltransferase (CHAT)-containing cells in the spleen that release acetylcholine which in turn binds to alpha 7 nicotinic acetylcholine receptor (α 7nAChR) on circulating monocytes, de-activating NF- κ B and thereby decreases pro-inflammatory cytokine release [26-28].

The vagus nerve also regulates both netrin-1 as well as pro-resolving lipid mediators [29]. Netrin-1, a neuronal guidance protein, limits leukocyte traffic during acute inflammation in peripheral organs and exerts anti-inflammatory and cytoprotective properties [30,31]. Through its location on blood-brain barrier endothelial cells, netrin-1 increases tight junction protein expression and reduces blood-brain barrier permeability [32].

Humoral mechanism can also resolve inflammation through the action of specific pro-resolving mediators (SPMs) such as lipoxins, resolvins, protectins, and maresins. These SPMs originate from fatty acids; for example, arachidonic acid gives rise to leukotriene A₄ which can be converted to either the pro-inflammatory leukotriene B₄ or the pro-resolution Lipoxin A₄ [33-35].

The other SPMs are generated from omega-3 polyunsaturated fatty acids via the intermediate compounds of eicosapentaenoic acid and docosahexaenoic acid [34]. The main function of the resolvins is to block neutrophils and monocytes migration and infiltration, thereby protecting tissues against immune cell-mediated injury. Resolvins also downregulate the expression of neutrophil adhesion molecules, reduce neutrophil oxidative burst, favor neutrophil apoptosis and clearance by macrophages, and participate in chemokine signaling termination by upregulating decoy receptors [36,37].

Blood brain barrier

The blood brain barrier (BBB) separates the peripheral circulation from the brain and its extracellular fluid [38,39]. Endothelial cells modulate barrier permeability by forming tight junctions

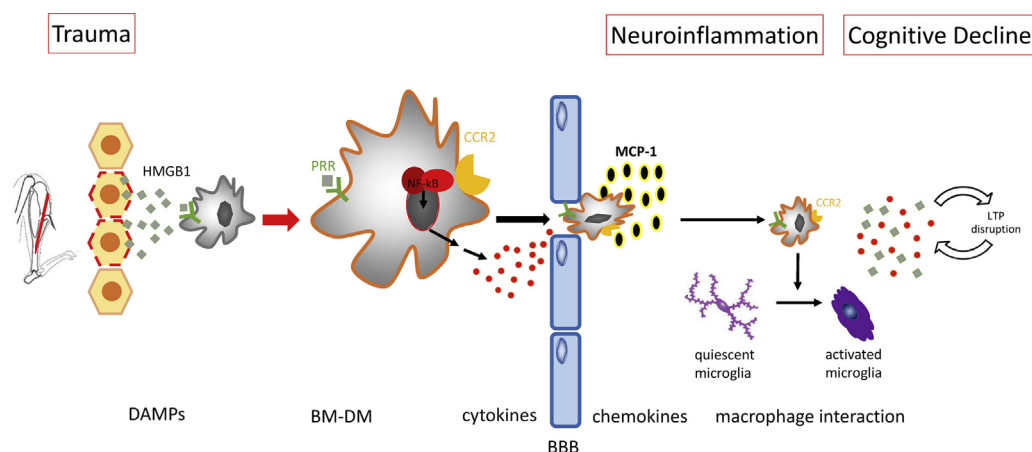


FIGURE 1

From left to right. Following peripheral trauma (indicated by the red intramedullary nail in a tibia that has been fractured), high molecular group box protein 1 (HMGB1) is passively released. This damage-associated molecular pattern (DAMP) binds to pattern recognition receptors (PRR) on circulating bone marrow-derived monocytes (BM-DMs) that signal to activate NF- κ B, a transcription factor that passes into the nucleus to cause increase expression and release of pro-inflammatory cytokines that are capable of disrupting the blood brain barrier. Within the brain parenchyma the chemokine MCP-1 (also referred to as CCL2) is upregulated and attracts the BM-DMs through binding to its cognate receptor, CCR2. In the presence of translocated CCR2-expressing BM-DMs as well as through other direct and indirect mechanisms the resident quiescent microglia become activated. Together, the BM-DMs and activate microglia release HMGB1 (a feed-forward mechanism) and pro-inflammatory cytokines that disrupt long-term potentiation (LTP) thereby blocking synaptic plasticity changes that are required for the cognitive functions of learning and memory

via transmembrane proteins such as claudins and occludins. These proteins eliminate space between the cells thereby limiting transfer of select products into and out of the brain through transport mechanisms within the cells themselves [32,40]. Inflammation disrupts BBB. The pro-inflammatory cytokine TNF- α activates the NF- κ B signaling pathway resulting in increased synthesis of prostaglandin E via upregulation of cyclooxygenase-2 (COX-2). The prostaglandins are capable of increasing the BBB permeability. Other pro-inflammatory cytokines, such as IL-1, utilize other signaling pathways that finally converge on COX-2 to produce the same effect [24,41-43].

Leukocyte migration into brain following peripheral surgery

Neither the human nor rodent brain parenchyma contains lymphocytes under normal conditions. Regarding the macrophage population within the brain parenchyma there are microglia but no dendritic cells [44]. Furthermore, there are perivascular macrophages, meningeal macrophages and choroid plexus macrophages, each with markers (Iba-1, F4/80) characteristic of the microglial phenotype [45]. The resident immunocompetent macrophage population is long-lived and is not replenished by myeloid-derived cells but may self-renew [46]. Within the healthy brain monocytes in the cerebrovascular circulation remain intravascular and cannot penetrate the blood brain barrier (BBB) [47]. Bone marrow-dependent monocytes

(BM-DMs) are present in large numbers in both chronic neurodegenerative conditions such as multiple sclerosis [48] as well as following acute neurologic injury such as stroke [49]. Following peripheral aseptic trauma expression of the chemokine MCP-1 (also known as CCL2) in the hippocampus is remarkably upregulated [15]; the source of the MCP-1 appears to be of both microglial [50] and astrocytic [51] origins. In a mouse model of peripheral inflammation microglia were shown to be instrumental at attracting BM-DMs into the brain [52]. Trafficking of the CCR2-expressing BM-DMs requires chemo-attraction by MCP-1 that binds to its cognate receptor, CCR2 [53]. Permanent engrafting of BM-DMs requires trafficking via chemokine receptors through a disrupted BBB. Following peripheral trauma, the BBB is impaired [41] allowing a massive infiltration of BM-DMs into the brain [50] where they produce a disease-enhancing role [54] that had been noted with other CNS lesions including stroke [55], traumatic brain injury [56] and status epilepticus [57]. Within the brain, the BM-DMs establish themselves and generate progeny with microglia-like appearance and become part of the brain's endogenous network of immune cells surveying tissue homeostasis. Interactions between the CCR2-expressing BM-DMs and the CX3CR1-expressing resident microglia are quite complex. In the MPTP-induced mouse model of Parkinson's Disease, elimination of CX3CR1 cells enhances inflammation and neurodegeneration [51,58]. Recent studies in a mouse model of postoperative

cognitive decline revealed a disease-reducing effect when CX3CR1 cells are depleted with a CSF-1 receptor antagonist [50].

Resident microglia

Role of the resident microglia

Microglia are yolk sac-derived and its migration into the CNS, prior to the formation of the BBB, is completed between embryonic days 8.5 to 9.5 in mice [59]. Microglia are crucially important during development involved in the phagocytosis of neural precursor cells especially in cortical proliferative zones [60]. Microglia are also involved in the synaptic pruning that occurs during brain development.

Under non-injurious conditions, CX3CL1 binds to its cognate receptor (CX3CR1) on microglia to maintain it in the inactive state [61]. In the adult brain, even in the resting ("quiescent") state, microglia subserve important functions involved in surveillance of brain parenchyma in order to maintain homeostasis [62]. Microglia elaborate and release a broad-spectrum of molecules, from cytokines to neurotransmitters and extracellular matrix proteins that can affect synaptic activity and functional plasticity [63].

Following release of pro-inflammatory cytokines by the innate immune response, microglia are activated by one or more of the following pathways. Cytokines can penetrate the BBB through leaky areas such as the circumventricular organs as well as via energy-dependent, saturable transport systems on brain endothelium. Peripherally-released cytokines can also indirectly stimulate microglia in the brain parenchyma via endothelial cytokine receptors or through afferent nerve fibers, such as the vagus nerve [64].

Irrespective of the pathway to activation, activated microglia can both be neuroprotective and neurotoxic [65]. Microglia are crucial for the phagocytosis of toxic products such as β -amyloid [66] but are also injurious in many disease states [67]. The ying-yang "protective-toxic" properties of activated microglia may be related to whether these cells exist in the classically-activated ("M1") or the alternatively-activated ("M2") state. However, that concept, i.e., M1 is pro-inflammatory and M2 is pro-resolving, is probably too simplistic an overview; rather the diverse nature of activated microglia should be distinguished on the basis of a "whole-genome expression in response to specific environmental challenges." [68].

As described above microglia play a crucial role in synaptic plasticity that produces the behavioral adaptation (for example learning and memory) to environmental signals [69]. Abnormalities in microglial signaling, through the absence of CX3CR1, will impair learning and memory as determined in the Morris water maze test [70].

Long-term potentiation

The conscious recollection of facts and events is referred to as declarative memory and long-term potentiation (LTP) is the

synaptic plasticity event that provides the neurobiologic underpinnings for this behavior [71]. As originally proposed by Cajal, the synaptic changes enhance the strength of the neuronal connections driven by coincidence between pre- and post-synaptic activity that is referred to as the Hebbian Model. Reduced to its basic elements, LTP is a long-lasting increase in strength at hippocampal excitatory synapses that requires post-synaptic depolarization – coupled to synaptic stimulation – as well as activation of post-synaptic NMDA receptors [72]. LTP is accompanied by both functional, detected electrophysiologically, as well as morphological, detected by enlargement of dendritic spines, changes [73].

LTP can be regulated by pro-inflammatory cytokines [74]. Pathophysiological levels of TNF- α inhibit LTP in the rat hippocampus [75] and TNF- α knockout mice demonstrate improved performance in spatial memory tests [76]. IL-1 β , another pro-inflammatory cytokine that is elevated in the hippocampus in models of postoperative cognitive decline [77], also interferes with spatial learning in the Morris water maze [78]. IL-1 β application also interferes with LTP and application of IL-1R antagonist enhances LTP in hippocampal slices [79]. However, it is likely that physiological levels of IL-1 β are required for LTP because IL-1R knockout mice display impaired performance in learning paradigms and do not express LTP [80].

Morphological changes

Because the pathogenic mechanisms for perioperative neurocognitive disorders are not defined there has not been a systematic attempt to determine the possible morphologic changes that either presage or enable a definitive diagnosis of this postoperative complication. However, this gap in knowledge is likely to be filled by data from two multicenter consortiums that are matching ancillary information to focused perioperative phenotyping. In the successful aging after elective surgery (SAGES) study, investigators subjected 137 elective surgical patients \geq 70 years of age to preoperative neuroimaging studies with a diffusion tensor sequence of an MRI scan [81]. Alterations in brain microstructural integrity, using diffusivity as well as global fractional anisotropy measurements, were strongly associated with the subsequent development of postoperative delirium suggesting a method of defining vulnerability [81]; this SAGES study corroborated an earlier small study involving 23 lung cancer surgical patients [82]. BIOCOG is an European consortium that seeks to validate biomarker panels (including neuro-imaging) for preoperatively predicting which non-cognitively impaired surgical patient is likely to develop postoperative cognitive impairment.

Based upon a plethora of evidence linking neuroinflammation to postoperative cognitive decline, its detection has been the subject of recent studies. In a case-control study involving 62 surgical patients that either did ($n = 31$) or did not ($n = 31$) develop delirium there was a strong association with

higher IL-6 levels [83]. Cape and colleagues [84] found a strong link between levels of CSF IL-1 β , at the time of induction of anesthesia, with the development of delirium following surgical repair of hip fracture. In a small study involving arthroplasty surgery, all 10 surgical patients accumulated pro-inflammatory cytokine in their postoperative CSF samples; in the single patient with delirium these levels were persistently high on sequential measurements [85]. Postoperative changes in a positron-emitting ligand for activated microglia was linked to postoperative cognitive changes [86].

Perioperative protection of the brain

Strategies designed to prevent and treat perioperative neurocognitive disorders seek to:

- identify modifiable patient- or disease-related risk factors that can be mitigated;
- pre-empt the pathogenic mechanisms especially in high-risk patients;
- identify and interrupt the pathogenic mechanisms prior to the development of cognitive decline;
- reverse ongoing cognitive decline.

Modifiable patient-related risk factors

Educational achievement

There is a very strong relationship between level of educational achievement and the risk of perioperative neurocognitive disorders. For every one-year increase in educational attainment, the risk for this postoperative complication declines by 10% [87]. Notwithstanding the fact that, like advanced age, educational achievement does not appear to be modifiable in the short-period prior to elective surgery, the Neurobics Trial is an ongoing study to determine the efficacy of cognitive exercises for 10 days preoperatively in reducing the incidence of postoperative delirium [88].

Physical exercise

Exercise has been shown to exert an anti-inflammatory effect [89]. Sedentary young adults (age 20–45) who were randomized to undergo high intensity aerobic exercise-training for 12 weeks showed a significant reduction in the monocyte production of TNF- α in whole blood *ex vivo*. A study of the impact of exercise on postoperative cognitive decline following surgery in a rat model of metabolic syndrome revealed a reduction in the exaggerated and persistent cognitive decline and this was associated with less systemic- and neuro-inflammation than in the non-exercise group [50].

Sleep

Sleep restores and repairs several mechanisms that are pivotal to learning and memory [90]. Slow wave sleep weakens the synaptic strengthening that occurs during wakefulness and restores the brain to a state that is capable of appropriately processing new sensory input in subsequent periods of wakefulness [91]. Obstructive sleep apnea, which grossly disturbs

sleep duration and depth, is associated with a significantly increase in postoperative cognitive decline [92]. In a small trial, improved actigraphically-assessed sleep reduced the prevalence of postoperative cognitive dysfunction [93].

Obesity and diet

Using a cut-off of a body mass index of 30, those that exceeded that index have an increased risk for postoperative cognitive dysfunction [87]. Diet-related attempts to mitigate this risk factor have focused on dietary supplementation with omega-3 polyunsaturated fatty acids that can be biotransformed into specific pro-resolving mediators (SPMs) [94,95].

Modifiable system-related risk factors

Multimodal interventions have shown considerable benefit in decreasing the incidence of postoperative delirium [96]. These common-sense, non-pharmacologic, delirium-reducing interventions such as having a dedicated geriatric "team" of care-providers, have changed the approach to acute hospital care of the elderly and have been quite successful at reducing the delirium-burden [97].

Pre-emptive therapy in high-risk patients

Identifying high-risk patients may result in customizing pre-emptive therapy to interrupt the pathogenic mechanisms. Currently, there are no preoperative tests to identify those surgical patients who lack the capacity to attenuate the innate immune system's inflammatory response. However, there are major advances being made in understanding the immunological profile of surgical patients that are likely to develop a postoperative inflammation-related complication [98,99].

Interrupting the inflammatory response

Etanercept

This antibody is directed against the pro-inflammatory TNF- α that is upregulated very soon after aseptic trauma [20,85]. When the organism is exposed to etanercept prior to surgery the inflammatory response is attenuated thereby preventing the development of postoperative cognitive decline; however, it is ineffective if the antibody is provided after the trauma has been initiated [20].

Anakinra

This recombinant protein blocks signaling through the IL-1 receptor thereby preventing the systemic and neuro-inflammatory responses to trauma [100]. In this manner, postoperative cognitive decline is aborted.

Tocilizumab

This antibody is directed against the IL-6 receptor. Exposure to this antibody will prevent blood brain barrier disruption and migration of BM-DMs into the brain parenchyma and thereby preventing the neuroinflammatory response as well as the development of postoperative cognitive decline [101].

These three biologic compounds have a side-effect profile that may be especially problematic in the perioperative period.

Interrupting the inflammatory pathway may interfere with wound healing [102]. Furthermore, the risk of infection is enhanced by the use of these biological agents. In the absence of a fool-proof method for identifying patients that are likely to benefit by interrupting the signaling of pro-inflammatory cytokines, its side-effects are probably too great a risk for routine administration.

Therapy to interrupt ongoing inflammation

As mentioned earlier, in the normal course of events the inflammatory response that is initiated by engagement of the innate immune response is attenuated by inflammation-resolving mechanisms that include both humoral and neural pathways. Before these strategies can be used, there must be a method for detecting the presence of an exaggerated and persistent inflammatory response in the postoperative period. While not available at present, recent advances in characterizing the innate immune response may hold the key to this treatment strategy [98].

Specific pro-resolving mediators (SPMs)

These are biotransformed products of arachidonic acid (e.g., lipoxinA₄) [103] docosahexaenoic acid and eicosapentaenoic acid (resolvins and maresins) [104]. Administration of aspirin-sensitive resolving D did limit postoperative cognitive decline [105].

Vagomimetic agents

Following the discovery that activation of vagal efferents can resolve inflammation [106], compounds designed to mimic these effects, including the use of agonists that activate the α_7 nAChR, have been successfully used to block neuro-inflammation and cognitive decline [41].

Dexmedetomidine, an imidazoline-ringed selective α_2 adrenergic agonist that has been shown to prevent postoperative delirium [107] appears to be effective by virtue of its vagomimetic action through the imidazoline ("I") receptor activity [108].

Acetylcholinesterase inhibitors such as physostigmine and neostigmine induce a vagomimetic action and have been shown to diminish postoperative neuroinflammation in an animal model of postoperative cognitive decline [109]; however, no behavioral studies were undertaken to determine the effects of acetylcholinesterase inhibitors on postoperative cognition. Nevertheless, this strategy should be further explored especially since anticholinergic drugs are known to increase the likelihood of postoperative cognitive decline [110].

Using a vagal nerve stimulator, Tracey's group has shown that this intervention dampens the peripheral inflammatory response [111]. As the use of these devices proliferate, it is likely to be introduced into the perioperative environment to tilt towards a vagomimetic-dominant autonomic nervous system response to surgery [112].

Therapy to reverse cognitive decline

After the onset of postoperative delirium, therapeutic strategies involve seeking and reversing specific risk factors including avoiding the use of benzodiazepines, opiates, and drugs with anticholinergic activity, improving sleep hygiene, as well as diagnosing and treating covert infections. For control of symptoms, several types of antipsychotic compounds have been investigated [113]. A recent meta-analysis of 12 randomized trials that investigated different anti-psychotics concluded that these do not improve outcome [114]. Use of anti-dementia compounds, such as donepezil has also been ineffective [115].

Future therapies

From preclinical studies, several juncture points in the pathogenic mechanisms are ripe for investigation. For example, if disruption of the blood brain barrier can be prevented, then neuroinflammation and cognitive decline may be prevented. Such a strategy may involve the use of compounds that resolve inflammation including α_7 nAChR agonists [116]. Another possibility may involve the use of selective ion channel blockers that prevent the activation of microglia [117].

Conclusions

We have highlighted the manner in which the brain is affected by the aseptic trauma of surgery to induce a major postoperative complication with devastating effects on the well-being and independence of surgical patients, especially for those of advanced age. The pathophysiologic mechanisms involve the initial engagement of the innate immune system in the periphery that launches an inflammatory cascade ultimately affecting synaptic plasticity in brain regions involved in learning and memory. On most occasions, homeostatic mechanisms involving neural and humoral inflammation-resolving pathways contain and reverse the functional effects of the peripheral trauma-induced neuro-inflammation. However, in some surgical patients the inflammation-resolving pathways are impaired and require interventions to appropriately restore homeostasis.

Future research should focus on identifying immunological traits that can inform both the likelihood of an individual patient developing postoperative cognitive dysfunction as well as the prompt diagnosis that inflammation is both exaggerated and/or persistent. Armed with this information, practitioners can customize interventions to tilt the risk-benefit analysis in favor of an improved postoperative outcome without adverse effects.

Acknowledgments: the authors gratefully acknowledge the assistance of Mr. Christopher Chang in the preparation of this manuscript.

Funding statement: authors' studies referred to in this manuscript were supported by the National Institutes of Health (R01GM104194). Dr. Sarah Saxena's work is funded by the Belgian American Education Foundation.

Disclosure of interest: the authors declare that they have no competing interest.

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