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Invited Review

Neuroinflammation is a putative target for the prevention and treatment of perioperative neurocognitive disorders

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Abstract

Introduction: The demographics of aging of the surgical population has increased the risk for perioperative neurocognitive disorders in which trauma-induced neuroinflammation plays a pivotal role.

Sources of data: After determining the scope of the review, the authors used PubMed with select phrases encompassing the words in the scope. Both preclinical and clinical reports were considered.

Areas of agreement: Neuroinflammation is a *sine qua non* for development of perioperative neurocognitive disorders.

Areas of controversy: What is the best method for ameliorating trauma-induced neuroinflammation while preserving inflammation-based wound healing.

Growing points: This review considers how to prepare for and manage the vulnerable elderly surgical patient through the entire spectrum, from pre-operative assessment to postoperative period.

Areas timely for developing research: What are the most effective and safest interventions for preventing and/or reversing Perioperative Neurocognitive Disorders.

Key words: neuroinflammation, surgery, cognitive decline

Introduction to perioperative neurocognitive disorders (PND)

The clinical problem

The aging of surgical patients as well as the increase in surgical volume, which will soon reach a quarter of a billion procedures,[1] have converged to provide the 'perfect storm' regarding the frequency of PND and the resulting increase in mortality and early retirement from the workforce.[2] Postoperative Delirium (POD) is the most common surgical complication among older surgical patients, occurring in between 15% and 25% following major elective surgery and considerably higher in susceptible patients undergoing hip-fracture repair and cardiac surgery.[3] The healthcare costs associated with these conditions are staggering; for example, a bout of POD can raise the in-hospital costs by between $16 000 and 64 000.[4]

Nomenclature

A plethora of non-standardized terms has been used to describe the spectrum of postoperative deterioration in cognitive performance that can differ according to time of onset, duration, severity, and the cognitive domains that are affected. The International Perioperative Cognition Nomenclature Working Group,[5] with expertize in postoperative medicine, cognitive neurosciences and epidemiology, coined the term Perioperative Neurocognitive Disorders (PND) that is both over-arching and aligned to the most recent Diagnostic and Statistical Manual of Mental Disorders (DSM V). Notwithstanding that the new semantic classification has yet to be ratified by the relevant medical societies, in this review we will use the encompassing term PND as the manuscript describing the new nomenclature has been published in the major journals in Anesthesiology (British Journal of Anaesthesia, Anesthesiology, Anesthesia and Analgesia, Acta Anaesthesiologica Scandinavica, Canadian Journal of Anaesthesia). Thus, PND denotes all the postoperative cognitive disorders including POD to reflect an acute onset and fluctuating course of inattentiveness, level of consciousness, and disordered thinking and, Postoperative Cognitive Dysfunction (POCD) to depict a longer-lasting decline in cognitive function from the preoperative status. As the diagnosis of POCD requires a deterioration from an established baseline, this condition is more established in the research domain because assessment of cognitive function is not yet a standard part of preoperative clinical management.

Pathophysiologic mechanisms

Apart from the requirement of a surgical procedure several other clinical circumstances have been proposed, and rejected, as pivotal requirements for the pathophysiology of PND; among the rejected clinical circumstances for the development of PND, include the type of anesthetic procedure (general vs. regional), as well as intra-operative physiological perturbations (especially, hypotension and hypoxemia).[6] Consideration of the putative mechanisms must explain the age-dependency, the increased risk in patients with metabolic syndrome patients, and in patients in whom an inter-current infection develops.

Supporting evidence for the neuroinflammatory basis of PND

Before describing the likely sequence of events that constitute the neuroinflammatory basis for PND, it is worth considering the systems, cell types and biochemical entities that are involved from surgical incision until cognitive decline.

Systems

The Immune System comprises the Adaptive and Innate arms with the latter dominating in the development of PND. Apart from the barrier functions provided by skin and mucosa, the Innate Immune System consists of cellular and chemical constituents that are the key elements to inflammation.

The blood–brain barrier (BBB) consists of both cellular and membranous components that form tight junctions thereby protecting the brain from the harmful effects of toxins and other detrimental products in the peripheral circulation.

Neuroplasticity is the basis for changing brain function whether it be for the better, e.g. learning and memory, or the worse, e.g. chronic pain. The key elements are the synaptic junction that includes both the presynaptic and postsynaptic neurones, the neurotransmitters that are released presynaptically and the postsynaptic signaling pathways that transduce the effect of the neurotransmitters.

Cells

Circulating in the peripheral blood are monocytes that are derived from haematopoietic sources such as the bone marrow; when these bone marrow-derived monocytes (BM-DMs) leave the circulation they assume the tissue macrophage phenotype that can be either pro-inflammatory (M1) or pro-resolving (M2).[7]

In the parenchyma of the brain are located the microglia, resident macrophages that had reached its destination during embryologic development before formation of the BBB. Microglia continuously survey the milieu responding to changes by adopting an M1 or M2 phenotype.

Damage-associated molecular patterns (DAMPs), cytokines and chemokines

These organic molecules are the originators, mediators and chemo-attractants that are required for the fully-fledged inflammatory response.

Lipoxins, resolvins, protectins and maresins

These are specialized pro-resolving mediators (SPMs) that are biotransformation products of polyunsaturated fatty acids and are required for the successful resolution of inflammation.

Proposed sequence of changes (Fig. 1)

The damage-associated molecular pattern (DAMP), known as high molecular group Box 1 protein (HMGB1), is released from the cytosolic compartment of traumatized tissue and engages the innate immune system by binding to pattern recognition receptors on BM-DMs to induce translocation of the transcription factor NFκB into the nucleus where it enhances the transcription and translation of pro-inflammatory cytokines.[8–10] The released cytokines are capable of disrupting the BBB, allowing the migration of both cells and potential neurotoxins, such as fibrinogen,[11] into the CNS. Translocation of BM-DMs into the brain is orchestrated by an upregulation of the chemo-attractant MCP-1 from microglia.[12] Within the CNS, the BM-DMs interact with microglia to release proinflammatory cytokines, such as IL-1β and IL-6 within the parenchyma; these cytokines can disrupt synaptic plasticity thereby preventing long-term potentiation, the neurobiologic correlate of learning and memory.[13,14] Resolution of self-limited inflammation is an active process; a combination of vagal activation that downregulates NFκB by signaling through α7 nicotinic acetylcholine receptors on immunocytes, and humoral factors especially the SPMs that transduce its signal through G protein-coupled receptors (GPCRs) which evoke rapid intracellular signaling and long-term actions by regulating specific microRNAs involved in resolution of inflammation.[15] Together these neural and humoral processes limit inflammation and restore cognitive function to the pre-morbid state.[16–18]

As mentioned above, any proposed pathophysiologic mechanism must explain the age-dependency and the increased risk in certain patient populations such as metabolic syndrome, and inter-current infection. Regarding age, it is notable that even at baseline (i.e. without any intervention) elderly subjects exhibit a low-grade inflammatory state that has been termed 'inflammaging'.[19] In an animal model of the metabolic syndrome, several deficiencies in the resolution of inflammation following aseptic trauma were noted.[20] To simulate an inter-current infection, a preclinical model explored the effect of introducing lipopolysaccharide (LPS), a constituent of the outer membrane of gram negative bacteria, to rodents that had undergone aseptic trauma[21]; again, excessive inflammation and exaggerated cognitive decline occurred. A recent meta-analysis explored the relationship between the degree of inflammation and PND and reported that levels of both c-reactive protein and IL-6 are

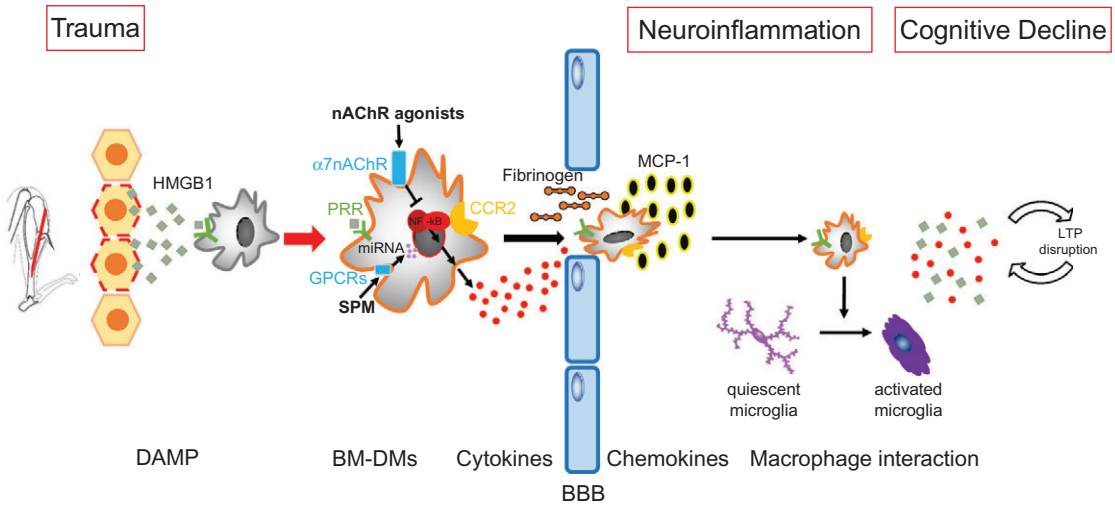

Fig. 1 A model for perioperative induced neuroinflammation and cognitive decline, and possible resolution. High molecular group Box 1 protein (HMGB1), a damage-associated molecular pattern (DAMP), is passively released from traumatized tissue during surgery. Through pattern recognition receptors (PRR) on circulating, CCR2-expressing, bone marrow-derived monocytes (BM-DMs), to induce translocation of the transcription factor NFκB into the nucleus where it upregulates the transcription and translation of pro-inflammatory cytokines. HMGB1 signaling also increases expression of monocyte chemo-attractant protein-1 (MCP-1) in the central nervous system (CNS) through an unknown mechanism. A cytokine-induced disruption of the blood–brain barrier (BBB) allows the migration of both cells and potential neurotoxins, such as fibrinogen, into the CNS. CCR2-expressing BM-DMs, attracted by MCP-1, reach the hippocampus where they transform quiescent microglia, the resident immunocompetent cells, into its activated form. Together, activated microglia and BM-DMs generate a neuroinflammatory response that interferes with long-term potentiation, the synaptic plasticity that is required for learning and memory. Normal resolution of inflammation is an active process that occurs through neural and humoral mechanisms. Neural involves vagal activation that downregulates NFkB by signaling through α7 nicotinic acetylcholine receptors (α7nAChR) on immunocytes. Regarding humoral factors, the specialized pro-resolving mediator (SPM), Resolvin D1, transduce its signal through G protein-coupled receptors (GPCRs) which evoke rapid intracellular signaling and long-term actions by regulating pro-resolving microRNAs (miRNA).

positively correlated with the prevalence and severity of PND.[22]

How does neuroinflammation produce cognitive decline?

This section will focus on the links between hippocampal neuroinflammation and synaptic and morphological plasticity that are required for successful learning and memory formation.

Synaptic plasticity

Activated microglia have a profound influence over synapse formation/elimination as well as its plasticity.[23] Apart from the disabling action of pro-inflammatory cytokines on long-term potentiation,[24] activated microglia also release reactive oxygen species that promote long-term depression.[25]

Morphological plasticity

The dentate gyrus portion of the hippocampus is one of only two regions in the mammalian brain that harbor regenerated neurons into adult life. It is notable that these neurogenic cells become integrated into hippocampal circuitry; approximately 700 adult-born hippocampal neurones are generated each day and contribute to its learning and memory functions.[26] Pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 interfere with integration and proliferation of adult hippocampal neurogenesis[27] and thereby prevent the morphological plasticity required for learning and memory.

Preventing neuroinflammation

The neuroinflammatory response to peripheral surgery appears to be an outmoded teleological defense mechanism that was probably designed to preserve animal life in the wild. To wit, if an animal had sustained an injury there needs to be a mechanism mitigating further damage and to facilitate the reparative processes; both the mitigation of further injury and the repair mechanisms are orchestrated by inflammation, centrally and peripherally, respectively. The mitigation of further injury appears to be orchestrated by neuroinflammation through the development of 'sickness behavior' that decreases appetite and procreative instincts while also producing fever, cognitive decline and fatigue.[28] An animal with the sickness behavior phenotype is unlikely to forage in the wild; rather, the injured animal will likely remain in a cool and non-threatening environment and thereby keep away from possible predators who can exploit their injured state.

In the case of aseptic surgical trauma to a hospitalized patient, neuroinflammation does not appear to be beneficial for rapid healing. In that context efforts need to be directed at limiting the neuroinflammatory response because of the possible harm that it can create. Mitigating strategies to prevent and/or limit neuroinflammation can be considered in three different phases, pre-operatively, intra-operatively and postoperatively. Also, the strategies can be designed to affect neuroinflammation indirectly (by limiting peripheral inflammation) and directly on the central inflammatory response while leaving the peripheral inflammatory response, and hence repair of the traumatized site, unhindered.

Preoperative pre-emption of excessive neuroinflammation

Exercise

That aerobic exercise has immune-modulatory properties was described more than three decades ago. Healthy young sedentary adult volunteers were randomized to a 12-week training program at either moderate or at high intensity which resulted in an improvement in aerobic capacity. Monocytes were harvested from peripheral blood and stimulated with lipopolysaccharide (LPS) and the release of tumor necrosis factor alpha (TNFα) into the medium was monitored. The high, but not the moderate, intensity training reduced LPS-induced release of TNFα into the culture medium.[29] These data suggest that immunocytes are re-programmed by exercise although the biologic processes involved were not identified.

To explore this finding further, use was made of metabolic syndrome rats—referred to as low-capacity runner (LCR) rats—that were shown to have an exaggerated and persistent form of postoperative cognitive decline[30] accompanied by an enhanced inflammatory response to the trauma of surgery.[20] The high-capacity runner (HCR) rats did not exhibit these abnormalities and served as the controls. The hypothesis was that preoperative exercise rectifies the abnormal inflammatory and cognitive phenotype following surgery and this was tested in a preclinical study.[31] Each of LCR and HCR rats was randomly assigned to four groups and subjected to isoflurane anesthesia and tibia fracture with internal fixation (surgery) or anesthesia alone (sham surgery) and to a preoperative exercise regimen that involved walking for 10 km on a treadmill over 6 weeks (exercise) or being placed on a stationary treadmill (no exercise). Cognitive tests were performed at 3 days as well as 3 months postoperatively. The previously observed exaggerated cognitive decline at both time-points was prevented by preoperative exercise in the LCR rats. Similarly, preoperative exercise normalized the excessive postoperative inflammation, both systemically and in the hippocampus. Interestingly, the diversity of the gut microbiome in the LCR rats improved after exercise. While the gut microbiome is shown to regulate the inflammatory response,[32] no causality could be attribute to exercise-induced change in the microbiome and improvement in postoperative cognitive decline. A clinical study (NCT3212300) to determine whether preoperative exercise decreases the risk for postoperative cognitive decline is underway.

Nutrition

Analogous to the situation of the metabolic syndrome (mentioned above), continuous high-fat diet

is associated with a chronic low-grade inflammatory state, referred to as meta-inflammation; a secondary response to this systemic inflammation is the activation of microglia.[33] A preclinical study examined the influence of a western diet on brain metabolism, transport across the BBB, inflammation and cognitive impairment in a mouse model of hyperlipidemia.[34] The authors reported that a western diet diminished cognitive processes and was associated with significantly increased BBB permeability as well as microglial Iba1 staining both of which are indicative of neuroinflammation. The western diet altered the whole mouse brain metabolome that included elevation of the proinflammatory lipid mediators.[34] Subsequently, it was reported that a high-fat diet, which induced obesity and insulin resistance, was associated with exaggerated postoperative cognitive decline and neuroinflammation.[35] Based upon these studies, investigators have used dietary manipulation to try to reverse the meta-inflammatory response. In an *in vitro* experiment, LPS-induced release of nitric oxide and IL-6 from a microglial cell line (BV-2 cells) was reduced when the culture medium included either omega-3 (docosahexaenoic and eicosapentaenoic) fatty acids or vitamins A and D. Moreover, the grouping of vitamins A and D, together with omega-3 fatty acids, each at concentrations where they individually had little effect, combined to significantly reduce LPS-induced nitric oxide release.[36] Four-week administration of omega-3 fatty acids to rats fed a high-fat diet decreased astrogliosis (GFAP-positive cells in the cerebral cortex) and pro-inflammatory cytokines but not in the hippocampus[37]; there was no improvement in cognitive decline.

Chunchai *et al.*[38] evaluated the effect of either prebiotic (Xylo-oligosaccharide), or probiotic (Lactobacillus paracasei HII01), or their combination (synbiotics), in male high-fat diet-induced obese rats. After 12 weeks of the high-fat diet, gut and systemic inflammation and impaired peripheral insulin sensitivity developed; these abnormalities were improved by each of the treatments.[38] Prebiotics, probiotics or synbiotics also improved hippocampal plasticity, attenuated brain mitochondrial dysfunction, decreased microglial activation and rectified cognitive dysfunction.

Based upon these studies, interventions that modify the preoperative diet may prove to be a viable strategy for decreasing risk in vulnerable preoperative patients. However, this needs to be tempered by the underwhelming results from interventional clinical trials with omega-3 fatty acids for a variety of inflammatory conditions.[39]

Perioperative pre-emption of excessive neuroinflammation

Sleep hygiene

Hospitalized patients are subjected to an environment that does not facilitate sleep. Zhu *et al.* investigated whether sleep deprivation, produced by a rocker inserted into the mouse cage for 24 h, can induce neuroinflammation and cognitive disturbance tested by Trace Fear Conditioning 1 and 7 days later.[40] Both hippocampal-dependent memory impairment and hippocampal neuroinflammation, as evidenced by pro-inflammatory cytokine IL-6 levels and microglial activation, were present 24 h after sleep deprivation and this state persisted for seven days after sleep deprivation. In a separate study,[41] sleep deprivation was associated with increased levels of systemic and hippocampal TNF-α, IL-1β, IL-6 and IL-8 as well as decreased hippocampal and systemic levels of anti-inflammatory cytokines (IL-4; IL-10). Vacas *et al.* explored the effects of 24-h pre-surgery sleep fragmentation in mice.[42] While sleep fragmentation did increase systemic IL-6 and transcription of TNFα in the hippocampus, it was not associated with a further deterioration in postoperative cognitive decline.

It is not recommended that benzodiazepines be used as sleep aids as this class of sedative-hypnotic does not produce the type of reparative and restorative sleep that is needed to resolve inflammation.[43] Interestingly, zolpidem, the non-benzodiazepine sleep aid, benefits patients with a variety of neurological disorders[44]; however, zolpidem has not been studied in the perioperative setting for mitigating PND.

Education

Patients with a higher education level are less prone to develop dementia although the post-mortem

examination of the brain did not reveal less neurodegenerative changes.[45] Higher educational attainment also was associated with less postoperative decline in a large cohort of elderly surgical patients.[6] An ongoing study is investigating whether engaging in preoperative 'mental gymnastics' could prevent delirium. The mental gymnastics consists of 1 h/day of electronic tablet-based cognitive exercise for 10 days prior to surgery (NCT02230605).

Reversing neuroinflammation

From Fig. 1, it becomes apparent that peripheral trauma-induced neuroinflammation can be addressed by either focusing interventions on processes in the periphery or the CNS. For the purposes of this review no further consideration is given to peripheral inflammatory targets because these are likely to interfere with wound healing.[46] Therefore, in considering methods of reversing neuroinflammation, this review will focus on the CNS processes that result in its onset (disruption of the BBB and translocation of circulating BM-DMs) and its propagation (pro-inflammatory transformation of macrophages).

Restoring the BBB

As disruption of the BBB is a pathognomonic feature of several acute (e.g. stroke), subacute (neuromyelitis optica) and chronic (multiple sclerosis) neurologic conditions, adoption of successful strategies in these diseases can also be considered in seeking ways of reducing surgery-induced neuroinflammation. Glucocorticosteroids (GC) can reduce BBB permeability in the setting of multiple sclerosis[47]; the mechanism may involve upregulation of the tight junction proteins claudin and occludin.[48] Interestingly, high-dose methylprednisolone was ineffective in preventing the development of postoperative delirium after cardiac surgery.[49]

Mesenchymal stromal cells (MSCs) reside in the perivascular space and are thought to be progenitors of pericytes that contribute to the neurovascular unit that defines the BBB. Following BBB disruption in a preclinical model of stroke, administration of MSCs resulted in increased expression of tight junction proteins and restoration of the barrier function.[50] Another method of upregulating tight junction proteins that has been tested in preclinical models is with laquinimod.[51] Also, statins can inhibit isoprenylation and also tighten the barrier function in disease models[52]; it is notable that a retrospective analysis of vascular surgery patients suggested that those receiving preoperative statins had a lower risk for developing delirium.[53] Erythropoietin (EPO) protects brain endothelium against VEGF-induced permeability by reducing the level of eNOS and restoring junctional proteins.[54]

APOε4 mice have a permeable BBB which can be reversed by inhibiting the pro-inflammatory cyclophilin A pathway[55]; however, inhibitors of cyclophilin A have yet to materialize into the clinical arena. Also, activated protein C can also improve endothelial barrier integrity[56]; again, this information has yet to be translated into clinical utility.

Fibrinogen/fibrin

Increased permeability of the BBB permits influx of the neurotoxin fibrinogen that is converted to fibrin through tissue plasminogen activator. Within the CNS fibrin binds to CD11/CD18 integrin receptor on tissue macrophages (both microglia and translocated BM-DMs) activating pathways[57] that include nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K), AKT (a serine–threonine protein kinase) and the Rho-family of GTPases. Through the activation of these pathways the following processes are affected including adhesion, migration, chemotaxis, phagocytosis and transformation into the M1 phenotype; when in the M1 phenotype the brain tissue macrophages release ROS, CCL2 (MCP-1) and CXCL10 that propagate further trafficking of BM-DMs, and T lymphocytes into the brain parenchyma. As fibrinogen/fibrin is necessary and sufficient for the induction/propagation of neuroinflammatory processes, this neurotoxin represents a potential target for reversing neuroinflammation.

While there are available compounds that deplete fibrinogen (ancrod) and promote the

degradation of fibrin (tissue plasminogen activator; tPA), these also can promote severe hemorrhage because of the key role that fibrinogen/fibrin plays in the coagulation pathway. Interfering with the interaction between fibrin and the integrin receptor, CD11b/CD18, on microglia with a 19 amino acid residue peptide fragment[58] inhibits its activation (PMID: 17339406). Fibrin can also interact with β amyloid and this can be prevented with RU 505 which also mitigates the neuroinflammation.[59] Trials to test the efficacy of these modulators of fibrin signaling are awaited.

Interrupting macrophage recruitment

The increase in circulating inflammatory factors can disrupt the BBB permitting translocation of CCR2-expressing BM-DMs into the hippocampus.[60] Within the hippocampus, the tissue macrophages become activated, synthesize and release pro-inflammatory cytokines that are capable of disrupting long-term potentiation. Treatment with CCX872, a novel CCR2 selective antagonist, significantly reduces TBI-induced accumulation of inflammatory macrophage, multiple proinflammatory and neurotoxic mediators and hippocampal-dependent cognitive dysfunction.[61]

Preventing macrophage activation

As microglial activation is a pathognomonic feature of neuroinflammation strategies to prevent its activation need to be further considered. 18β-Glycyrrhetinic acid is a major metabolite of glycyrrhizin a constituent of some traditional Japanese medicines; this compound has been shown to inhibit microglial activation in a model of autoimmune encephalomyelitis[62] and attempts to use this to block liver inflammation in clinical trials have not been successful. There are three major types of K+ channels on microglia: K_V 1.3, K_{ir} 2.1 and K_{Ca} 3.1 current. Both K_V 1.3 and K_{Ca} 3.1 blockers, PAP-1 and TRAM 34 respectively, inhibit pro-inflammatory cytokine production and iNOS and COX2 expression demonstrating that these ion channels play important roles in microglia activation.[63]

Transforming macrophage phenotype from M1 to M2

There are several possible therapeutic candidates for conversion into the pro-resolving M2 macrophage phenotype. Fumarates prevent microglial activation through a novel hydroxycarboxylic acid receptor-2 and dampen neuroinflammation[64]; dimethyl fumarate (Tecfidera®), which is biotransformed to the active monomethyl fumarate, has been shown to be clinically useful in MS patients and is available for further exploration in other clinical settings including PND. JWH133, a selective cannabinoid receptor-2 (CB2) agonist, suppresses neuroinflammation by modulating microglial polarization to the M2 phenotype through activation of the protein kinase A (PKA) pathway.[65] As other cannabinoids (CB1 agonists) are progressing through clinical trials it is possible that selective CB2 agonists may also become available for conditions such as PND. Acting via the PGC-1α pathway, resveratrol promotes the conversion of microglia to the M2 phenotype; importantly, resveratrol attenuated both LPS-induced neuroinflammation and sickness behavior.[66] Two recently completed, but as yet unreported, clinical trials have explored the clinical potential of resveratrol in the setting of cognitive decline; a positive demonstration of its efficacy *vs* cognitive decline may result in extension to PND.

Conclusion

Current evidence strongly supports targeting neuroinflammation for the prevention and reversal of perioperative neurocognitive disorders. Extrapolating from other neurological disorders, such as multiple sclerosis and Alzheimer's Disease in which neuroinflammation plays a prominent role, there are several possible interventions both pharmacological and non-pharmacological. Clinical trials are needed to test the efficacy and safety of these interventions.

Conflict of interest statement

The authors have no potential conflicts of interest.

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