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Anesthetic modulation of neuroinflammation in Alzheimer's Disease

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Abstract

Purpose of review—To summarize key studies and recent thought on the role of neuroinflammation in chronic neurodegeneration, and whether it can be modulated by anesthesia and surgery.

Recent findings—A large and growing body of evidence shows that neuroinflammation participates in the development of neurodegeneration associated with Alzheimer's disease. Modulation may be possible early in the pathogenesis, and less so when cognitive symptoms appear. A dysfunctional hypo-inflammatory response may permit accelerated damage due to other mechanisms in late disease. The peripheral inflammatory response elicited by surgery itself appears to provoke a muted neuroinflammatory response, which enhances ongoing neurodegeneration in some models. Anesthetics have both anti- and pro-inflammatory effects depending on the drug and concentration, but in general, appear to play a small role in neuroinflammation. Human studies at the intersection of chronic neurodegeneration, neuroinflammation, and surgery/anesthesia are rare.

Summary—The perioperative period has the potential to modulate the progression of chronic neurodegenerative diseases. The growing number of elderly having surgery, combined with the expanding life expectancy, indicates the potential for this interaction to have considerable public health implications, and call for further research, especially in humans.

Keywords

neurodegeneration; surgery; perioperative neurotoxicity; cytokines; cognitive dysfunction; microglia

Introduction

The role of inflammatory pathways in the brain, termed neuroinflammation, in the pathology of the neurodegenerative disorders, or even normal aging processes, remain unclear, but evidence to date suggest they participate. It is somewhat more apparent that events during the perioperative period can modulate these pathways, and thus impact the chronic, ongoing pathogenesis operant in disorders like Alzheimer's disease. Such perioperative events include the anesthetic, surgery itself, a myriad of other drugs, pain and potentially sepsis. Finally, it is very clear that the elderly are the largest consumers of operative, or procedural care, thus the mechanistic intersection between Alzheimer's, aging, operative care and

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inflammation is of importance. This review briefly considers the concepts, and examines recent studies that lend insight into these interactions and possible underlying mechanisms.

Neuroinflammation

Similar to peripheral inflammation, the process in the central nervous system (CNS) has both cellular and humoral mediated mechanisms. The primary cell of interest is the microglial cell, derived from myeloid precursors in the bone marrow during embryogenesis [1]. Under normal physiological conditions, microglia are in a resting state, evenly distributed throughout the brain with a characteristic star-like morphology. They have varied age-dependent functions, including brain development, synaptic plasticity, immune surveillance, and repair. These cells respond to a wide variety of stressors, including ischemia, trauma, and pathogens, in part via specific signaling molecules, such as pro-inflammatory cytokines, reactive oxygen (ROS) and nitrogen species, chemokines, complement, and heat shock proteins, by becoming activated [2]. When so activated, they move to affected areas (such as areas of cell injury or apoptosis), and undergo morphological changes to resemble macrophages. This change heralds phagocytosis by the activated microglia, and the production of cytokines, chemokines, growth factors, and ROS [3]. The origin, fate and repletion of microglia are incompletely understood, but it is thought that certain cells (e.g., monocytes) can move from the periphery into the brain, especially in situations that disrupt the blood brain barrier (BBB), to participate in these processes, and perhaps become microglia [2]. The other major brain cell type that responds to the same stressors is the astrocyte. Reactive astrogliosis is a common finding in areas of the brain damaged by ischemia, infection or misfolded protein deposits, focal lesions or trauma [4]. Cross talk between these reactive cells and neurons via a large array of signaling molecules is complex and incompletely understood.

Neuroinflammatory responses can be both detrimental and beneficial [5]. On the one hand, activated microglia clear apoptotic or injured cells, dysfunctional synapses, and amyloid-β plaque, and with astrocytes, promote repair via secretion of neurotrophic factors and produce anti-inflammatory cytokines, such as interleukin-10 (IL-10). The timing and regionality of the humoral response is important to its success at protection. On the other hand, microglial activation is accompanied by an immune response and the expression of pro-inflammatory proteins, such as interleukin-beta and interleukin-6 (IL-1β , IL-6) and tumor necrosis factor alpha (TNF-α), whose exuberance can lead to the damage of normal neurons, and signaling processes through recruitment of other cells that generate an ROS response. The result is synaptic and neuronal dysfunction, manifest ultimately by cognitive dysfunction. Cognitive disturbance resulting from systemic inflammation alone has been well documented [6], although the precise mechanisms for this acute, and often transient cognitive dysfunction is unclear and might be distinct from that underlying Alzheimer's disease. The balance between the beneficial and detrimental effects of neuroinflammation is crucial to the outcome, and thus factors capable of modulating aspects of the process are important to understand.

Neuroinflammation and Alzheimer's disease

Although the precise orchestration remains unclear, neuroinflammation is a hallmark of neurodegenerative disorders like Alzheimer's disease. This has long been suspected because of the observation that those taking chronic anti-inflammatory drugs (e.g. for arthritis) had a lower incidence and/or later onset of Alzheimer symptoms [7]. Indeed, randomized trials based on these observations have confirmed the salutary effects of certain non-steroidal anti-inflammatory drugs, such as ibuprofen, although the later the drug is started with respect to

symptoms or age, the less effective it becomes [8;9]. This might be the explanation for the minimal benefit from anti-inflammatory medication while symptomatic.

The brains of patients afflicted with neurodegenerative disorders are characterized by increased numbers of activated microglia and astrocytes and elevated pro-inflammatory protein levels, such as IL-6 and TNF-α [3]. Microglia and inflammatory proteins are physically associated with amyloid-β plaques in the brain pathology of AD patients, a feature that has suggested that extracellular amyloid-β is an important activator of microglia [5]. It remains unclear whether the amyloid-β needs to be in the soluble oligomeric form, or as a fibril clump (the senile plaque) to initiate microglial activation, but in vitro studies have suggested the former [10–12]. It is likely that the microglial activation is initially protective, in that the misfolded protein is degraded and cleared. Whether Alzheimer's disease is largely due to the ongoing amyloidopathy (and tauopathy), or the brain's inflammatory response to the presence of these abnormal proteins, or to dysfunctional, hypoactive microglial responses, remains unclear. Both Alzheimer's disease and the ongoing neurodegeneration, or the aging process alone, seems to "prime" microglia for exaggerated responses to inflammatory signals [13]. For example, aging is characterized by a significant increase in activated microglia, inflammatory proteins and complement factors [13;14]. The induction of peripheral inflammation using lipopolysaccharide (LPS) in aged [14–18] and Alzheimer model animals [19–22] elicits in the brain a larger cytokine response, tau phosphorylation and microglial activation than in young or WT animals, thereby resulting in cognitive dysfunction. The cytokine response may actually result in a positive feedback loop by enhancing the expression of the amyloid precursor protein and increasing cellular and secreted levels of amyloid-β [23]. Some secreted cytokines, such as IL-4 and Il-10 may be protective. For example, over-expression of IL-4, an anti-inflammatory cytokine, in the brain of Alzheimer model animals reduces progression of the neuropathology [24]. Inflammatory proteins spill over into the cerebral spinal fluid (CSF) of Alzheimer patients, including monocyte chemoattractant protein-1, interleukins and C-reactive protein [25], although neither consistently or specifically enough to be considered biomarkers. The only accepted biomarkers for Alzheimer's disease at this point are the CSF levels of amyloid-β and total tau [26].

It has been recently proposed that inflammatory dysfunction, rather than hyperactivity, contributes to neurodegeneration. A recent study of isolated microglia suggests that those from aged animals, while constitutively secreting more IL-6 and TNF-α than those from young animals, are actually less responsive to stimulation from amyloid-β [27]. Microglial degeneration and dysfunction leads to loss of microglial protection and defective amyloid-β clearance [28] and could thereby contribute importantly to Alzheimer's neuropathology [2;28]. The resulting accumulation of abnormal extracellular protein may then destroy processes directly, such as axons and synapses, and perhaps in parallel lead to the characteristic lesion of Alzheimer's disease, the senile plaque. Age alone may also be associated with reduced microglial (and neuronal) function. Nevertheless, recent genome-wide association studies have identified two genes, CLU and CR1, which encode for clusterin and complement receptor 1, that are associated with an increased risk of developing late-onset Alzheimer's disease [29]. Both genes are involved in amyloid-β clearance and the regulation of inflammation. When combined with the above evidence, this suggests that inflammation plays at least a supporting role in Alzheimer disease pathology.

In addition to the central nervous system immune system effects on Alzheimer's disease, Alzheimer's disease may directly affect the peripheral immune system. For example, amyloidopathy (not necessarily amyloid-β) of peripheral organs, such as the heart, kidneys and gut [30–33] also occurs in Alzheimer disease [34;35], which itself may stimulate an inflammatory response. Furthermore, IL-1β and IL-6, was found to be elevated in the blood

from Alzheimer's disease patients compared to controls, which was significantly correlated with cognitive impairment [36;37]. Thus, a bi-directional interaction between the peripheral and the CNS immune system may play an important role in Alzheimer's disease.

Neuroinflammation and Surgery

The two principle aspects of surgery that could impact both inflammation and cognition are the anesthesia and the actual operation or procedure, aspects that we will address separately.

Anesthesia

While evidence supports that local anesthetics, especially lidocaine, have anti-inflammatory properties [38;39], it is less clear whether general anesthetics can modulate inflammation. Several studies have demonstrated that isoflurane alone attenuates both peripheral and CNS inflammatory markers (e.g. IL-1β , IL-6, TNF-α, microglia) after LPS injection [40–43], but other studies report that the same drug, given alone, enhances the baseline level of these same inflammatory markers in the brain up to 24 hours afterward [44]. Other studies have failed to detect any changes in either cytokines or microglia following general anesthesia with inhalational or intravenous drugs alone [45–48]. These disparate results might be reconciled by the wide array of very different drugs that can be called, "general anesthetics". For example, ketamine, a still widely used "dissociative" intravenous general anesthetic, has stronger evidence of anti-inflammatory properties [40] than other general anesthetics, especially the inhalational ones. Differences may also be due to the various doses and durations employed, and the baseline level of inflammation present. Thus, while the drug alone may cause a mild inflammatory response in the absence of an ongoing inflammatory process, it may also blunt the response to a profound stimulus, such as LPS. There is ample precedent for such context-sensitive drug responses.

Potential mechanisms for anesthetic effects on immune or inflammatory function include alterations in the BBB permeability [49;50], alterations in monocyte recruitment [51] and direct interactions with a vast array of the involved signaling molecules, such as the integrins [52;53]. For example, a crystallographically identified site for isoflurane and sevoflurane on the LFA-I domain of integrin stabilizes a conformer with low affinity for its receptor, suggesting these drugs will inhibit an important upstream event in the inflammatory cascade. Given the promiscuity of our inhalational drugs, it is surprising that little attention has been paid to the potential direct effects on other signaling molecules or their receptors, such as the interleukins.

Surgery

It is well established that surgery causes a profound systemic inflammatory response, in a rough relation to the magnitude of tissue damage [54]. However, the translation of this robust peripheral response to the brain appears to undergo significant dampening, probably because most of the humoral factors are produced in the periphery and are short-lived, and also because they encounter the BBB. However, cytokines may gain entry to the CNS in BBB deficient or damaged areas [55], or may be actively transported or transduced by endothelial cells [56]. It is relevant to note that vasculitis is a common feature of ongoing neurodegeneration such as Alzheimer's disease, a feature that alone compromises the BBB [57]. Once having gained entry into the CNS, directly or indirectly, these signals trigger the neuroinflammatory response, probably by initially activating microglia. This inflammatory response to surgery is enhanced by age [58;59] and can be prevented by a variety of anti-inflammatory compounds. To what extent this surgical induction of neuroinflammation provokes cognitive dysfunction is not clear, but the importance is suggested by the clinical

observation that post-operative cognitive dysfunction (POCD) and occurs independent of the anesthetic approach used (inhalational, intravenous or regional) [60].

Surgery, inflammation, POCD and Alzheimer's disease

Although the discussion above considers many of these features in isolation, it is clear that they will co-exist in many of our patients. The existence of cognitive decline after surgery is reasonably well-established [61], although some have recently questioned this consensus because of significant methodologic issues in prior work [62]. Apart from the existence, the mechanism, magnitude and durability of cognitive dysfunction after surgery are poorly understood. For example, is POCD an enhancement (or unmasking) of Alzheimer-like neuropathology? Is it reversible? Whatever the character and mechanism, it seems very likely that surgery-induced inflammation is involved in POCD, and perhaps in a central manner. For example, in humans, CSF inflammatory biomarkers were elevated after coronary artery bypass surgery (CABG) [63;64] and were associated with subsequent cognitive decline. Further, CSF amyloid-β and tau changed in a direction consistent with Alzheimer's disease 6 months after CABG surgery, whether performed with inhalational or intravenous anesthesia [65].

Most of the evidence for an interaction between surgery, POCD, Alzheimer's disease and inflammation comes from animal studies. For example, in young WT mice, surgery (either tibial osteoplasty or splenectomy), and not anesthesia, caused both neuroinflammation and acute cognitive losses [45;47;48] and both microglial activation and cognitive deficits were reduced by anti-inflammatory agents. It is noteworthy that if the anesthetic was isoflurane, a small degree of neuroinflammation and cognitive dysfunction was noted, in comparison to injectable drugs, where none was elicited. In another study, the inflammatory and cognitive effects of partial hepatectomy was found to be greatly enhanced in older animals, and associated with elevated hippocampal pro-inflammatory cytokines [59].

Few animal studies have specifically examined Alzheimer neuropathology following anesthesia and surgery. In a recent example, partial hepatectomy in 14 month-old wild-type mice provoked microgliosis, astrogliosis, amyloid-β accumulation and tau hyperphosphorylation out to 7 days post-operatively. This was prevented by an anti-inflammatory compound (celastrol) given perioperatively [66]. Very few such animal studies have evaluated the long term consequence of either anesthesia or surgery. In our laboratory, we found that anesthesia alone could enhance plaque load in the old Tg2576 mouse, a well-established murine model of Alzheimer disease, only a week after exposure [67], and in a more recent triple transgenic mouse model [68] that recapitulates the amyloid and tau neuropathology, we found an increase in tau neuropathology after anesthetic exposures prior to cognitive decline [69]. Increased TNF-α levels have also been reported in the brains of neonatal AD transgenic mice after exposure to sevoflurane [46]. Durable tau hyperphosphorylation was also detected after isoflurane exposure in a mouse model with tauopathy [70]. Furthermore, we have found that abdominal surgery (cecal ligation and excision) in the triple transgenic mouse promotes a very durable (3 months) decline in cognition that is associated with both tau pathology, microgliosis and elevations in IL-10 (unpublished results). The anesthetic (30 minutes of desflurane) had only a transient effect on cognition, and no detectable effect on inflammation.

Conclusion

It would appear that anesthesia alone causes only a modest initiation of neuroinflammation, which may be dependent on the drug used. It seems that isoflurane is consistently provocative, while the injectable drugs such as ketamine and possibly propofol are less so.

Surgery, on the other hand, stimulated a robust peripheral and somewhat less robust CNS inflammatory response. This appears to have the potential to cause a short term POCD on its own, and a more durable cognitive effect in the setting of a brain made vulnerable by either age or ongoing neurodegeneration.

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Key Points

- Neuroinflammation plays a key role in Alzheimer disease, although the timing, regionality, and modifiable period remain unclear
- Anesthesia alone may modulate inflammatory cascades, but the demonstrated effects so far have been modest.
- Surgery has a more profound effect on the peripheral inflammatory response, provoking neuroinflammation.
- In late aging and Alzheimer's disease, neuroinflammation may become dysfunctional, leading to loss of protection and greater neurodegeneration.
- In light of the huge numbers of patients receiving surgery every year, and the prevalence of cognitive complaints, there is ample opportunity to study this issue in humans.