JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Opinion

Surgery, Neuroinflammation and Long-Term Outcome

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It has long been known that patients often experience a state of confusion following surgery, classified as delirium or postoperative cognitive dysfunction (POCD). Although this surgery-induced cognitive dysfunction may predict the progression of dementia in elderly patients, there is little known about the relationship between surgical trauma and the development of chronic neurodegeneration. Recent population evidence suggests that surgery increases the risk of dementia (1), but the biological mechanisms behind this (and related therapeutic targets) are not yet to be fully understood.

Surgery and Neuroinflammation

The mechanical injury caused by surgery anywhere in the body triggers inflammation, which is a protective mechanism of the innate immune system. Even without infection at the site of the surgical lesion, many different leukocytes are activated and mobilised, including monocytes and macrophages. These cells in turn release a variety of signalling molecules such as nitric oxide (NO), prostaglandins and pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, which amplify local response to systemic response. This systemic inflammatory response following surgery is well documented, and is proportional to the extent of surgical insult. Excessive peripheral inflammation, however, can cause damage at distant locations and directly affect the central nervous system (CNS). The blood brain barrier is not as impermeable as previously thought and it is now known that pro-inflammatory molecules alter the integrity of this barrier and allow the entry of leukocytes and many other cells and molecules into the brain (2, 3).

This surgery-induced neuroinflammation not only alters blood brain barrier function, but also causes glial cells to propagate this inflammatory response via cell signalling molecules such as cytokines. Microglia, the resident macrophages of the brain, transform from an inactivated state to an activated, phagocytic one when stimulated by pro-inflammatory cytokines (4). These cells can remain activated for long periods of time, contributing to long-term degeneration (5). Microglia also express major histocompatibility complex (MHC) class 1 and MHC class 2, which although are usually implicated in infectious diseases, can contribute to neurodegeneration (6). Astrocytes can also be stimulated and release pro-inflammatory molecules such as TNF-α, and these cells combined with activated microglia and blood brain barrier endothelium, propagate a considerable inflammatory response.

This response is mediated by an array of signalling molecules. Some, such as cytokines TNF-α and interleukin (IL)-1β are largely pro-inflammatory whereas others can dampen down neuroinflammation. The situation is complicated by the fact that different concentrations of the same molecules can have different effects on glia and neurons. One way in which the direct effects of these molecules is shown is in TNF's role in mediating apoptosis and neuronal damage through the production of caspase-8 (7).

The cyclooxygenase (COX)-1 pathway has been shown to cause excessive prostaglandin synthesis in microglia, resulting in cognitive impairment and neurodegeneration (8). Glycogen synthase kinase-3 (GSK3) is a protein that has been recently recognised as having pro-inflammatory properties in the brain. It stimulates the migration and activation of microglia (9) and stimulates these cells to produce TNF-α via nuclear factor (NF)-κB (10) and NO (11). GSK3 levels are also related to blood brain barrier permeability and an increase of GSK3 levels increases leukocyte entry across this barrier (12).

Adverse Effects of Neuroinflammation

Neuroinflammation caused by surgery can bring about synaptic impairment, which damages neurons beyond repair long before apoptosis and adversely affects the formation and retention of memories. An example of a neuroinflammatory mechanism is high levels of IL-1β causing a loss of

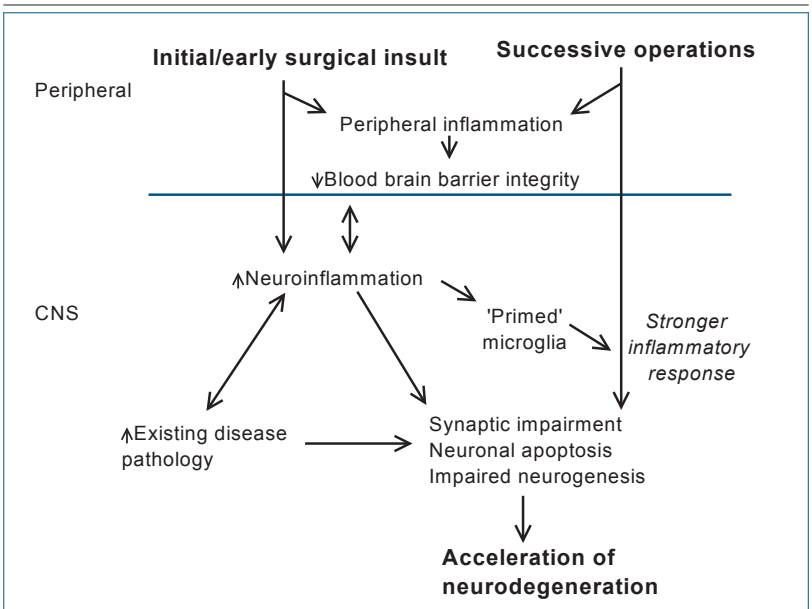

Figure. The Contribution of Surgery to Neurodegeneration. Repeated procedures may exacerbate the damage caused by previous neuroinflammation.

synaptic connections through sensitisation of NDMA receptors to glutamate in pre- and post-synaptic terminals (13). Neurogenesis, which is the development of neurons from neural progenitor cells, is also damaged by neuroinflammation. Although limited to a small area of the hippocampus in adults, damage to neurogenesis is associated with cognitive dysfunction and is seen in early and late stages of dementia (14). A reduction in neurogenesis is seen in early, pre- symptomatic Alzheimer's disease, suggesting a relationship between the reduction of this process and the progression of dementia. Pro- inflammatory cytokines such as IL-6, TNF-α and IL-18 inhibit neurogenesis (15). Neuroinflammation not only brings about the death of neural progenitor cells but also plays a part in neuron apoptosis. This can be brought about by high levels of NO and cytokines (16, 17).

The discovery that microglial cells can be 'primed', much in a similar way to macrophages in the peripheral immune system (18), has significant relevance for the development of acute inflammation to chronic neurodegeneration. Priming is the process of cell sensitisation to an initial insult, resulting in augmented inflammatory responses when stimulated by successive waves of inflammation. Peripheral inflammation can bring about these exaggerated responses from primed microglia in the CNS (19-21).

Surgical Damage from Short-Term to Long-Term: An Example with POCD and Alzheimer's Disease

POCD can occur in a patient of any age following major surgery, and even minor operations can cause POCD in the elderly (22). Major surgery has been shown to induce strong inflammatory responses that are key in the signalling process leading to cognitive change and decline. For example, surgery causes a rise in levels of inflammatory cytokines such as IL-1β and other inflammatory markers, which results in short- term cognitive dysfunction (23). The use and duration of anaesthetics also plays a significant part in the development of POCD, but it is clear that inflammation caused by surgical trauma is a causative agent of the condition.

In elderly patients, POCD can predict the future onset of dementia and evidence suggests that repeated surgery and anaesthesia contribute to long- term neurodegeneration. Neuroinflammation can hasten the development of Alzheimer's disease pathologies such as tau phosphorylation (24) and Aβ synthesis (25). Inflammation outside of the CNS, in the form of IL-6 and IL-10, can damage the integrity of the blood brain barrier and allow the crossing of Aβ and its precursors into the brain. The relationship between surgery-induced inflammation and irreversible, long-term damage, however, may not simply follow a cause-and-effect model, but instead involve numerous self- propagating cycles (Figure). This is noticeably shown in the production of IL-6 by Aβ peptides and the stimulation of amyloid precursor protein (APP) (and resulting pathology) by IL-6 (26, 27). Episodes of POCD following surgery can also be 'acute- on- chronic', with the short-term outburst of symptoms resulting from underlying long-term neurodegeneration. Neuroinflammation poses a greater risk of POCD to those with dementia than those without an existing pathology, and it is likely that repeated surgical insults accelerate the development of Alzheimer's

disease and other conditions.

Although it is likely that acute-on-chronic episodes contribute to the disease process of long-term neurodegeneration, the relationship between surgery-induced neuroinflammation and the advancement of early, pre-symptomatic dementia is unclear. A unique and interesting proposition, however, involves the microglial priming model. Using Alzheimer's disease as an example, Aβ peptides stimulate NADPH oxidase mediated priming in microglia, leading to a neurotoxic release of reactive oxygen species (28). Many inflammatory triggers are released in the early stage of Alzheimer's disease (29) and over long periods of time this could result in the priming of microglia. A subsequent trigger, in the form of surgery and anaesthesia, could activate these primed glia cells, amplifying the neuroinflammatory reaction (20) and accelerating neurodegeneration. Surgery itself could further prime microglia via glucocorticoids (30), suggesting that the neuroinflammation may become progressively worse over successive operations.

Conclusion

Tissue damage caused by surgery invokes an inflammatory response that is often amplified from local to systemic. Research into the associations between surgery and the onset of neurodegenerative diseases and elucidation of many inflammatory pathways in the brain is just beginning. Nevertheless, in order to protect patients with existing pathologies and prevent surgery increasing the risk of developing dementia in asymptomatic patients, perioperative care research must look for ways of attenuating surgery-induced neuroinflammation (31).

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Citation: Monty Lyman, Da-Qing Ma. Surgery, neuroinflammation and long-term outcome. *J Anesth Perioper Med* 2014; 1: 122-4.

1. Chen PL, Yang CW, Tseng YK, Sun WZ, Wang JL, Wang SJ, et al. Risk of dementia after anaesthesia and surgery. Br J Psychiatry 2014; 204: 188-93.
2. Laflamme N, Lacroix S, Rivest S. An essential role of interleukin-1beta in mediating NF-kappaB activity and COX-2 transcription in cells of the blood-brain barrier in response to a systemic and localized inflammation but not during endotoxemia. J Neurosci 1999; 19: 10923-30.
3. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol 2011; 70: 986-95.
4. Liu X, Wu Z, Hayashi Y, Nakanishi H. Age-dependent neuroinflammatory responses and deficits in long-term potentiation in the hippocampus during systemic inflammation. Neuroscience 2012; 216: 133-42.
5. Liu B, Hong JS. Role of microglia in inflammation-mediated neurodegenerative diseases: mechanisms and strategies for therapeutic intervention. J Pharmacol Exp Ther 2003; 304: 1-7.
6. Al Nimer F, Beyeen AD, Lindblom R, Ström M, Aeinehband S, Lidman O, et al. Both MHC and non-MHC genes regulate inflammation and T-cell response after traumatic brain injury. Brain Behav Immun 2011; 25: 981-90.
7. Kischkel FC, Lawrence DA, Chuntharapai A, Schow P, Kim KJ, Ashkenazi A. Apo2L/TRAIL-dependent recruitment of endogenous FADD and caspase-8 to death receptors 4 and 5. Immunity 2000; 12: 611-20.
8. Matousek SB, Hein AM, Shaftel SS, Olschowka JA, Kyrkanides S, O'Banion MK. Cyclooxygenase-1 mediates prostaglandin E(2) elevation and contextual memory impairment in a model of sustained hippocampal interleukin-1beta expression. J Neurochem 2010; 114: 247-58.
9. Yuskaitis CJ, Jope RS. Glycogen synthase kinase-3 regulates microglial migration, inflammation, and inflammation-induced neurotoxicity. Cell Signal 2009; 21: 264-73.
10. Wang MJ, Huang HY, Chen WF, Chang HF, Kuo JS. Glycogen synthase kinase-3beta inactivation inhibits tumor necrosis factor-alpha production in microglia by modulating nuclear factor kappaB and MLK3/JNK signaling cascades. J Neuroinflammation 2010; 7: 99.
11. Huang WC, Lin YS, Wang CY, Tsai CC, Tseng HC, Chen CL, et al. Glycogen synthase kinase-3 negatively regulates anti-inflammatory interleukin-10 for lipopolysaccharide-induced iNOS/NO biosynthesis and RANTES production in microglial cells. Immunology 2009; 128: e275-86.
12. Ramirez SH, Fan S, Zhang M, Papugani A, Reichenbach N, Dykstra H, et al. Inhibition of glycogen synthase kinase 3beta (GSK3beta) decreases inflammatory responses in brain endothelial cells. Am J Pathol 2010; 176: 881-92.
13. Mishra A, Kim HJ, Shin AH, Thayer SA. Synapse loss induced by interleukin-1β requires pre- and post-synaptic mechanisms. J Neuroimmune Pharmacol 2012; 7: 571-8.
14. Kuhn HG, Dickinson-Anson H, Gage FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. J Neurosci 1996; 16: 2027-33.
15. Liu YP, Lin HI, Tzeng SF. Tumor necrosis factor-alpha and interleukin-18 modulate neuronal cell fate in embryonic neural progenitor culture. Brain Res 2005; 1054: 152-8.
16. Harry GJ, Lefebvre d'Hellencourt C, McPherson CA, Funk JA, Aoyama M, Wine RN. Tumor necrosis factor p55 and p75 receptors are involved in chemical-induced apoptosis of dentate granule neurons. J Neurochem 2008; 106: 281-98.
17. Bal-Price A, Brown GC. Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. J Neurosci 2001; 21: 6480-91.
18. Frank MG, Baratta MV, Sprunger DB, Watkins LR, Maier SF. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav Immun 2007; 21, 47-59.
19. Cunningham C, Wilcockson DC, Campion S, Lunnon K, Perry VH. Central and systemic endotoxin challenges exacerbate the local inflammatory response and increase neuronal death during chronic neurodegeneration. J Neurosci 2005; 25: 9275-84.
20. Cunningham C, Campion S, Lunnon K, Murray CL, Woods JF, Deacon RM, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. Biol Psychiatry 2009; 65: 304-12.
21. Murray C, Sanderson DJ, Barkus C, Deacon RM, Rawlins JN, Bannerman DM, et al. Systemic inflammation induces acute working memory deficits in the primed brain: relevance for delirium. Neurobiol Aging 2012; 33: 603-616. e3.
22. Rosczyk HA, Sparkman NL, Johnson RW. Neuroinflammation and cognitive function in aged mice following minor surgery. Exp Gerontol 2008; 43: 840-6.
23. Cibelli M, Fidalgo AR, Terrando N, Ma D, Monaco C, Feldmann M, et al. Role of interleukin-1beta in postoperative cognitive dysfunction. Ann Neurol 2010; 68: 360-8.
24. Krstic D, Madhusudan A, Doehner J, Vogel P, Notter T, Imhof C, et al. Systemic immune challenges trigger and drive Alzheimer-like neuropathology in mice. J Neuroinflammation 2012; 9: 151.
25. Chen CH, Zhou W, Liu S, Deng Y, Cai F, Tone M, et al. Increased NF-kappaB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. Int J Neuropsychopharmacol 2012; 15: 77-70.
26. Jana M, Palencia CA, Pahan K. Fibrillar amyloid-beta peptides activate microglia via TLR2: implications for Alzheimer's disease. J Immunol 2008; 181: 7254-62.
27. Ringheim GE, Szczepanik AM, Petko W, Burgher KL, Zhu SZ, Chao CC. Enhancement of beta-amyloid precursor protein transcription and expression by the soluble interleukin-6 receptor/interleukin-6 complex. Brain Res Mol Brain Res 1998; 55: 35-44.
28. Schilling T, Eder C. Amyloid-beta-induced reactive oxygen species production and priming are differentially regulated by ion channels in microglia. J Cell Physiol 2011; 226: 3295-302.
29. Vukic V, Callaghan D, Walker D, Lue LF, Liu QY, Couraud PO, et al. Expression of inflammatory genes induced by beta-amyloid peptides in human brain endothelial cells and in Alzheimer's brain is mediated by the JNK-AP1 signaling pathway. Neurobiol Dis 2009; 34: 95-106.
30. Frank MG, Thompson BM, Watkins LR, Maier SF. Glucocorticoids mediate stress-induced priming of microglial pro-inflammatory responses. Brain Behav Immun 2012; 26: 337-45.
31. Vizcaychipi MP, Watts HR, O'Dea KP, Lloyd DG, Penn JW, Wan Y, et al. The therapeutic potential of atorvastatin in a mouse model of postoperative cognitive decline. Ann Surg 2014; 259: 1235-44.