Decline in cognitive function after surgery (commonly termed, the postoperative cognitive dysfunction syndromes, or POCDS) is a phenomenon of increasing importance to the current focus on long-term outcomes of healthcare (1, 2). Concerns over the POCDS have been raised at the extremes of life. For example, children having more than 3 surgeries before the age of 3 may be at risk of both behavioral and intellectual compromise later in life (3, 4). Furthermore, in the elderly, anesthesia and surgery have been suggested to contribute to the development of delirium and Alzheimer disease (AD), and yet, if true, it is unclear whether anesthesia, or surgical stress itself is the trigger (5, 6). But to put this into perspective, the occurrence of POCDS at the extremes of age may be related to particular vulnerabilities associated with development and/or aging. The immune system contributes substantially to these vulnerabilities, especially in the aging brain. Here, we will briefly review how and why the immune responses of the central nervous system (CNS) can conspire with anesthesia and surgery to produce durable dysfunction.

Surgery, Anesthesia and Peripheral Inflammation

The severity of the POCDS results from several factors (Figure). Some individuals are more prone to release higher levels of inflammatory cytokines than others due to the slightly genetic differences. Also, pre-existing cognitive status plays an important role. Type and duration of surgical stress is critical, but its effect could be heavily influenced by anesthesia. Whereas one could hypothesize that anesthetics trigger inflammation, most evidences suggest the opposite (7-9). Thus, it seems likely that the surgery itself initiates inflammatory events that could lead to decline in cognitive function (9, 10). Some studies further support this notion, showing no differences in the incidence of POCDS between general and regional anesthesia (11, 12). It is well known that surgery causes peripheral tissue damage, pain and inflammation, called the systemic inflammatory response syndrome (SIRS). SIRS is of course beneficial to some degree in that, it allows wound healing and pathogen elimination. SIRS is heralded by increased serum levels of interleukin-1 beta (IL-1β), IL-6, tumor necrosis factor-α (TNF-α) and prostaglandins, all of which will reach the brain. When combined with vagal afferent stimulation, an ability of surgery to provoke inflammation in the brain is strongly suspected, and it is less clear that this is beneficial. There exist good preclinical evidences for neuroinflammation after surgery and after injection of lipopolysaccharide (LPS); there also exist limited human evidences that proinflammatory cytokines are elevated in the cerebrospinal fluid (CSF) after even minor stress (13). More data are available in animal models but they remain to be seen how these finding will translate into clinical reality (3, 10). Our prior attempts to transfer promising treatment in animals, especially sepsis, were frequently unsuccessful. Whether anesthetics can moderate this peripheral inflammatory response before they reach the brain remains unclear, and may depend strongly on the classifications of drugs used (e.g., alkylphenol or haloether), and other modulating circumstances.

Activation States in Microglia

In the brain, the major cells responsible for activation of the immune response are the microglia. These cells share numerous common features with mononuclear monocyte/macrophage system. However, they are an ontologically distinct population originating from unique progenitor cells during embryonic brain development (14). Microglia constantly monitor their local microenvironment. They recognize pathogens or sig-
nals via a number of receptor types, such as the conservative toll-like receptors (TLR). Under normal physiological conditions, these cells serve as sentinels and remain quiet and dormant. Their nascent state is maintained by several inhibitory cytokines, such as transforming growth factor β type (TGFβ), CD200R cytokines, and CX3C chemokine receptor 1 (CX3CR1). During stress state, similar to the peripheral monocyte, microglia can be activated by virtually any disturbance in local microenvironment. Their activation depends on the type of stimuli, nature of brain damage and type of tissue degeneration. Activation of the microglia leads to a powerful and exaggerated release of cytokines (IL-6, TNF-α, etc.) compared to the peripheral response (15). This exaggerated response makes brain much more vulnerable to inflammation induced damage.

The mechanisms of microglia deactivation are virtually unknown. Outside the CNS, SIRS is extinguished via several mechanisms including apoptosis, removal of the offending pathogen or injury and/or activation of compensatory anti-inflammatory responses (CARs). CARs has numerous subcomponents. For example, release of inhibitory cytokines, such as IL-10, macrophage colony-stimulating factor (M-CSF), TGFβ, an increase in the fraction of immunomodulatory cell populations like Treg, Th2, Th17, or an evolution of the innate inflammatory response into a more focused acquired mechanism (dendritic cells, clonal selection of T and B cells). These peripheral resolution mechanisms are less apparent in the brain. Microglia deactivation is induced by IL-10 and TGFβ but this effect may be attenuated in aging brain (16, 17). Suppression of microglia activation, or their deactivation, is critically important because an initiation of the inflammatory process inside CNS frequently leads to synaptic and neuronal damage, events that may not be reversible and presumably lie upstream of POCDS (18).

Microglia Priming Accelerates Degenerative Processes in Brain
Microglia can become "sensitized" to activation by sub-threshold stimuli, such as seepage of pathogens or cytokines through the blood brain barrier (BBB), or misfolded proteins that accumulate as a result of neurodegenerative disorders. This process of enhanced sensitivity to stimulation is called priming. Microglial priming can also be induced by ingestion of apoptotic bodies, and it has been shown in preclinical models that apoptosis is triggered by inhalational anesthetics like isoflurane. If primed microglia are exposed to a subsequent stimulation, such as surgery, the inflammatory response is much stronger and prolonged. We believe that activation of the microglia can become a self-sustained phenomenon, in part because of an inability to deactivate it. The process then becomes a positive feedback loop; inflammation of the CNS leads to a smoldering degenerative process that primes the microglia, with their subsequent activation further exacerbating CNS injury. If this perfect storm occurs in a brain with limited reserve, and/or with pre-existing vulnerabilities like apolipoprotein E-ε4 (Apo-E-ε4), more damage and the consequent cognitive sequelae would be expected. This process is similar in its nature to the overwhelming sepsis-related SIRS in the periphery.

Endothelial Process Contributes to Progression of AD
The BBB represents an impor-
tant structural mechanism protecting the brain and its microglial sentinels from peripheral pathogens and inflammatory signals. It is formed by the cerebrovascular endothelium, and its integrity is maintained by endothelial cell tight junctions. This provides a remarkably effective shield, by retarding diffusion of compounds such as the inflammatory cytokines from blood into CNS. However, endothelial cells are sensitive to the inflammatory stimulus, and may try to make themselves produce and release cytokines stimulating microglia without a breach in the BBB. To make matters worse, the endothelial inflammatory processes will then open tight junctions and thereby increase permeability of the BBB, so that cytokines can gain direct access into the brain. Further, inflammatory cells such as neutrophils and macrophages can now enter usually restricted space of brain. Neutrophils are short-lived cells and their effect will be limited to acute damage. On the other hand, monocytes can reside for prolonged periods of time in the brain. These inflammatory monocytes exhibit a higher secretion of TNF-α, especially the membrane-bound form, numerous cytokines and reactive oxygen species (19-21). These processes damage neurons and astrocytes, and activate microglia. Since these inflammatory monocytes can persist in the brain for long periods of time, the damage can be substantial (20).

Chronic diseases and aging-related changes may also compromise the BBB, which simply amplifies the effect of a stress like surgery or infection. For example, cerebral vascular endothelial cell dysfunction and leukocyte transmigration across the BBB are described as early events in the development of AD and vascular dementia. We strongly suspect that these pre-existing compromises of the BBB, coupled with microglial priming by smoldering inflammatory processes, set the stage for a stressful event to produce neuronal damage, and if extensive, the consequent decline in cognitive function.

**Proteinopathy Further Propels Inflammation**

The pathological hallmarks of AD are the accumulation of Aβ peptides in the brain as extracellular senile plaque, and the intracellular accumulation of tau aggregates termed neurofibrillary tangles. It is not yet clear how or why Aβ monomers aggregate into oligomers, and then deposit as plaques, or why this occurs in selected regions of the brain. It is also not clear whether this represents an increase in production and a decrease in clearance; both may occur. The inhalational anesthetics have been reported to both accelerate the production and promote the aggregation of Aβ (22), and events associated with surgery, such as hypothermia, appear to promote the aggregation of Tau. It is clear that these proteinopathies can enhance microglia and macrophage activation and induce secretion of proinflammatory cytokines and chemokines. It is also observed that proteinopathies can activate microglia surrounding the senile plaque and perivascular amyloid deposits. With respect to the latter, it seems likely that these events could be implicated in the degeneration of the BBB. Whether anesthetics have direct influences on tight junctions or the BBB, remains unclear.

**Conclusion**

In this short commentary, we attempt to convey the message that inflammation is well-positioned to be a major contributor of CNS pathology that may lead to the various forms of POCD. The combined influence of pre-existing pathology and a second hit from surgery and inflammation could very well provoke an unrestrained sequence of events that are responsible for the cognitive pathology documented over the last few decades. Critical questions that remain unsolved are the role of anesthesia (anesthetics), whether resolution mechanisms are intact, and whether anti-inflammatory or pro-resolving strategies can be designed to mitigate POCD. Hampering progress has been the lumping of all cognitive disturbances as "POCD". It is certainly possible that delirium and acutely reversible POCD have different underlying mechanisms and pathologies compared to dementia or AD. Biomarker studies in human would help to provide a mechanism-based approach to diagnosis, terminology and ultimate treatment of POCD.

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