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...
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.
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, β 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).