Neural and Immune Consequences of Traumatic Brain Injury

Does Propofol Reduce the Impact?

In this issue of Anesthesiology, Luo et al. provide evidence that propofol dampens microglial activation after traumatic brain injury and that this leads to improved neurological outcomes in the rodents they studied. This work adds to accumulating data about the organ-protective effects of anesthetics and their effects on the immune system. Although the neuroprotective effects of propofol have been shown several times, the improvement in cognitive outcomes relative to isoflurane is intriguing. One interpretation is that propofol may be neuroprotective by directly decreasing microglial activation through modulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidation reactions after traumatic brain injury; however, we should be cautious in accepting this sole conclusion.

First, although the antiinflammatory effect of propofol may directly promote neuroprotection via dampening of microglial activation, further work is required to establish a causal link. Indeed propofol's in vivo mechanism of protection is not studied or established in this work; though a correlation between a dampened microglial response and improved cognitive outcome is observed. Understanding the immune effects of anesthetics and sedatives is an important clinical agenda that may impact upon a wide range of outcomes including traumatic brain injury, delirium, long-term cognitive impairment, and infection. This is supported by recent data showing associations between sedative medications and delirium, as well as associations from animal data between surgery and anesthesia (and concomitant inflammation) with worse outcomes. In this regard, Luo et al.'s work may have impact beyond their tightly controlled experimental paradigm.

Second, species differences always require cautious extrapolation especially given differences in rodent and human immunity and physiology. Third, the comparator anesthetic chosen was isoflurane (that is rarely used in critical care); hence, the relative immune effects of other drugs, with differing mechanisms of action, such as $\alpha_2$ adrenergic agonists remain unclear. Indeed, $\alpha_2$ agonist neuroprotection has been observed in in vitro models of traumatic brain injury. Fourth, propofol was applied in a clinically relevant medium, intralipid, but it is unclear whether this contributed to the observed effects as vehicle controls were lacking in vivo. Intralipid itself has been associated with immune modulatory activity. Ideally, another control group, animals not under anesthesia but having an infusion of intralipid, would have been included. Understandably, this was not considered ethical. In vitro, vehicle controls were used; however, there was no isoflurane treatment group—limiting comparison with the in vivo data. Fifth, the anesthetic drugs were given before and during the traumatic brain injury—a situation that rarely occurs in reality. Understanding the effects of drugs 1 or 2 h after traumatic brain injury would have greater clinical relevance but again this may not be possible ethically. Finally, the use of immortalized cells in the in vitro work further distances the findings from the clinical arena.

"Anesthesiologists are increasingly turning their attention to anesthetic effects on organs other than the brain—the immune system may be the most important and deserves our focus."

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The authors justify their use of these cells, but the clinician must recognize these immortalized cells are different from mouse microglia and do not represent an exact substitution.

There are several strengths to the authors’ work that equally deserve mention. The authors perform several control experiments, such as excluding γ-amino-butyric acid type A (GABA<sub>A</sub>) receptor signaling as part of propofol’s microglial-suppressing mechanism. The authors also study the mechanism of microglial suppression in depth, identifying propofol’s effects on NADPH enzyme activity as well as expression of NADPH subunits. The use of a wide range of propofol concentrations in vitro is also of interest as the ideal neuroprotective dose of propofol to study, based on the limited data about brain concentrations of propofol in humans, remains unclear.19 Perhaps of most importance, the cognitive tests used imply a functional difference in rodents, a critical step in establishing whether a treatment may have impact on future clinical studies.

Based on this work, one proposal is that patients with traumatic brain injury, who require sedation, may benefit from being treated with propofol—an assertion that needs further testing. Other sedatives, such as α2 agonists,9 must be explored. Another hypothesis could be that suppressing microglial responses with propofol may have utility in limiting surgery-induced inflammatory brain injury.13–15,20,21 Perhaps, total intravenous anesthesia may be associated with reduced delirium and postoperative cognitive decline compared with inhaled anesthesia? Although the data so far do not support this proposal,22 further studies of the effect of anesthetic technique on perioperative brain injury are required.

Mechanistically, the possibility that propofol modulates microglial function through GABA<sub>A</sub> receptor signaling is excluded though the authors acknowledge some contribution to the immune effects observed. This is important, as previous studies suggest that propofol’s anesthetic and neuroprotective action23,24 is blocked by GABA<sub>A</sub> antagonists,24 but Luo et al. found that propofol’s microglial effects are not. These inconsistencies necessitate further research.

Other GABAergic drugs than propofol, such as benzodiazepines and zopiclone (“Z” drugs), exert significant clinical immune effects predisposing to infection.25,26 and leading to increased mortality from infection.27,28 Many immune cells express GABA<sub>A</sub> receptors. GABA<sub>A</sub> receptor activation on macrophage induces intracellular acidosis with impaired inflammatory responses, phagocytosis, and bacterial killing.9 In vivo diazepam treatment increases mortality in mice from Streptococcus pneumoniae infection,9 an effect reversed in vivo with the GABA<sub>A</sub> antagonist bicuculline,9 indicating a GABAergic mechanism. Neutrophils do not express GABA<sub>A</sub> receptors;9 hence their function is unaffected by other GABAergic modulators.27 However, the generation of free radicals through NADPH oxidase is critical for neutrophilic bacterial killing; hence, the potential for propofol to increase susceptibility to infection is also worthy of consideration.28 Given that propofol exerts direct effects on NADPH oxidase, it may exert additional effects on neutrophil function compared with other GABAergic drugs.28 This may manifest as an increased risk of infection with propofol sedation or anesthesia—another hypothesis that is worthy of investigation.

Many anesthetic and sedative drugs modulate GABA<sub>A</sub> receptor signaling. Although we readily recognize the significant neuronal effects of these drugs, the ramifications of their immune effects are not yet understood. If dampened microglial function comes at a price of impaired neutrophil function, the increased risk of infection may outweigh the benefits of this type of sedation. Given the significant contribution of infection to outcomes in traumatic brain injury, and other critical illnesses, we must be cautious how we apply our drugs.

Like many good studies, Luo et al.’s data stimulate more questions than definitive answers. Clinicians should not change their practice based on this study, but we hope that it will stimulate their thought on how their drugs are applied. Anesthesiologists are increasingly turning their attention to anesthetic effects on organs other than the brain—the immune system may be the most important and deserves our focus.

Robert D. Sanders, B.Sc., M.B.B.S., Ph.D., F.R.C.A.,* Mark Coburn, M.D.,† Pratik P. Pandharipande, M.D., M.S.C.I., F.C.C.M.;‡ *Department of Anaesthesia and Surgical Outcomes Research Centre, University College London Hospital and Wellcome Department of Imaging Neuroscience, University College London, London, United Kingdom. r.sanders@ucl.ac.uk. † Department of Anesthesiology, University Hospital RWTH Aachen, Aachen, Germany. ‡ Department of Anesthesiology, Division of Critical Care, Vanderbilt University Medical Center, Nashville, Tennessee.

References


