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Separating the effects of anaesthesia and surgery on the brain

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Cognitive disorders have been reported to follow anaesthesia and surgery in older individuals for more than 130 years.[1] Intuitively, since anaesthetic agents act on the CNS, it was assumed these agents must be the primary cause of any alterations in an individual's cognitive state occurring with a temporal association to anaesthesia and surgery. In fact, two seminal papers in this field did not question this assumption, with Savage[1] in 1887 entitling his work 'Insanity following the use of anaesthetics in operations' and Bedford[2] in 1955 entitling his 'Adverse cerebral effects of anaesthesia on old people'. More recently the importance of the impact of the inflammatory response and underlying patient vulnerability has been emphasised.[3] The work by Deiner and colleagues[4] in this issue of the *British Journal of Anaesthesia* adds to this body of knowledge and suggests our assumptions may have led us to limit our interpretations and investigations of possible mechanisms from the beginning.[4]

Preclinical work has revealed deleterious effects of volatile anaesthetics on memory in rodents and an increase in biomarkers associated with Alzheimer's disease.[5] More recent work implicates peripheral inflammation leading to neuroinflammation as possible pathophysiology, but definitive studies, especially in humans, are lacking.[6] Preclinical work has also shown increases in inflammatory biomarkers including tumour necrosis factor-α (TNF-α) associated with anaesthesia and surgery, but when anaesthesia alone was administered there was no such inflammatory response,[7] implicating surgery as the inducer of the inflammation. How do we separate the effects of anaesthesia and surgery in humans when the two almost always occur together? The work by Deiner and colleagues[4] is an important step forward in our understanding of the specific effects of anaesthesia in the absence of inflammation driven by surgically-induced tissue injury.

Perioperative neurocognitive disorders include postoperative neurocognitive disorder (previously known as postoperative cognitive dysfunction), postoperative delirium, or both.[8] Several studies have reported an increase in cytokines associated with postoperative delirium and postoperative neurocognitive disorders, but it is only recently that the possible downstream effect of neuroinflammation, neuronal damage, has been found to occur in association with anaesthesia and surgery.[9] This work showed an increase in biomarkers of neuronal damage, namely neurofilament light (NF-L) and tau, associated with anaesthesia and surgery. The cognitive sequelae associated have not been reported, but the increases observed in this small cohort are in line with increases observed with mild acute traumatic brain injury in sports players.[10]

There have been indications that anaesthesia may not be the primary cause of perioperative neurocognitive disorders. For example, the incidence of postoperative cognitive dysfunction at 3 months was similar after cardiac surgery, noncardiac surgery, or light sedation, suggesting the type and duration of anaesthesia itself did not have a major impact on cognitive outcomes.[11] Similarly, studies comparing regional anaesthesia and general anaesthesia have not reported a difference in the incidence of cognitive outcomes.[3] Further, a study investigating general anaesthesia *vs* spinal anaesthesia without sedation found that patients undergoing extracorporeal shock-wave lithotripsy had a similar incidence of postoperative cognitive dysfunction at 3 months regardless of anaesthesia type. In fact, per protocol analysis of that study suggested general anaesthesia resulted in a lower incidence of postoperative cognitive dysfunction compared with spinal anaesthesia without sedation. Although this work needs to be interpreted carefully given the likelihood that the inflammatory stimuli of extracorporeal shock-wave lithotripsy, without surgical incision, is low, it does support the work by Deiner and colleagues[4] whereby perioperative neurocognitive disorders are not specific to type of anaesthesia.[12] After originally being attributed to cardiopulmonary bypass,[13] many studies were undertaken to investigate on-pump *vs* off-pump cardiac surgery, leading to further evidence that cardiopulmonary

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bypass itself was not solely responsible for longer term postoperative cognitive disorders (when assessed some months after surgery).[14,15] More recent work has shown a similar incidence of perioperative neurocognitive disorders after light sedation for left heart catheterisation.[16]

This leads us to enquire more deeply into the effect of anaesthesia *per se* on biomarkers of neuronal injury in humans. Deiner and colleagues[4] report on inflammatory and neuronal damage biomarkers in participants undergoing MRI under ~2 h of general anaesthesia with sevoflurane after induction with propofol, the first such study in humans to investigate inflammatory and neuronal injury biomarkers in general anaesthesia without surgery.[4] They report a significant increase in interleukin-6 from baseline to post-anaesthesia, but no change in TNF-α or C-reactive protein. The authors also undertook plasma analysis for markers of neuronal damage including NF-L, tau, and glial fibrillary acidic protein. As noted, both NF-L and tau have been shown to increase in patients undergoing anaesthesia and surgery akin to changes seen with traumatic brain injury.[9] Although tau may be derived peripherally and from the CNS, previous work has shown close correlation between plasma and CSF analysis of both NF-L and tau.[9,17] Samples were obtained pre-anaesthesia and 2 h after anaesthesia, which Deiner and colleagues[4] suggest approximates sampling times reflective of the work by Evered and colleagues[9] in patients undergoing anaesthesia and surgery, however a slow increase by some biomarkers may not be detected at this time. However at this timepoint, Deiner and colleagues[4] did not see any increase in these markers of neuronal injury when anaesthesia alone was administered, a strong implication that surgery, rather than anaesthesia, is responsible for the neuroinflammation, and by implication, downstream neuronal damage reported in patients undergoing anaesthesia and surgery. This conclusion supports the work by Berger and colleagues[17] that showed that increases in tau were independent of type of anaesthetic.

Although informative, this study has several limitations. The study included only 59 healthy volunteers across a wide age range, with <40% more than the age of 60 yr, which limits application of these results to the cohort of patients who most frequently experience perioperative neurocognitive disorders. As patients with pre-existing cognitive impairment are at greater risk of perioperative neurocognitive disorders, and it would appear that this study did not include any such vulnerable patients, these results must be viewed with some caution in terms of prior probability. The authors frankly note they experienced an unexpected freezer malfunction resulting in some samples exposed to room temperature for 24–36 h which could have impacted their results, although they reassure us that this is not the case. However, noting the relatively small numbers, the data provided in the Supplementary material do raise questions regarding these sensitive assays and possible freeze-thaw changes in TNF-α and site-specific differences in assay results for tau and C-reactive protein. Averaging values across the two different analytic laboratories merits further consideration. The authors report neither the data for the duration of anaesthesia, nor the time until postoperative testing, limiting the interpretation of the results, especially as previous work has noted the time-sensitive nature of the responses for neuronal injury markers as far as 48 h postoperatively. It is also possible that the increase observed in interleukin-6 derived from peripheral sources rather than the CNS. Finally, it should be recognised that two anaesthetic agents were used in these cases, with propofol induction followed by sevoflurane maintenance; therefore, the results should be interpreted in that context.

Further work is critical both to confirm the biomarker changes associated with anaesthesia and surgery, and to confirm the absence of these increases with anaesthesia alone. It would be of value to identify if certain anaesthesia agents were actually protective to the brain in the surgical inflammatory environment. Importantly, we need to understand the clinical correlates and how the concentrations of these biomarkers relate to perioperative neurocognitive disorders in the short and long terms. The work by Deiner and colleagues[4] is an important contribution to our understanding of the impact of anaesthesia alone on the brain, and uniquely aids our understanding of mechanisms underlying perioperative neurological biomarker changes.

Authors' contributions

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Manuscript editing and revisions: LE, DAS
Manuscript contributions to second and subsequent drafts: DAS

Declarations of interest

LE is a member of the associate editorial board of the *British Journal of Anaesthesia*.

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Targeting microglia to mitigate perioperative neurocognitive disorders

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Perioperative neurocognitive disorders, including acute postoperative delirium and delayed neurocognitive recovery or postoperative cognitive decline (POCD), represent major health concerns for elderly patients undergoing anaesthesia and surgery.[1] These disorders are associated with poor long-term outcomes, increased healthcare costs, and increased mortality.[1,2] The lack of effective treatments place a tremendous burden on patients, their families, and our society. Thus, novel therapies are needed to prevent or treat these disorders.

In this issue of the *British Journal of Anaesthesia*, Lai and colleagues[3] postulate that Kv1.3 channels, which belong to the super-family of voltage-gated potassium (Kv) channels, are promising drug targets to mitigate POCD. The goal of their study was to determine whether inhibiting Kv1.3 channels expressed in microglia prevented POCD. The results raise interesting questions that are significant to the field of anaesthesiology, especially given the emerging role of microglia in POCD.

Microglia are the resident immune cells in the brain, where they account for about 10–15% of all cells.[4] Potassium channels, including Kv1.3, are important regulators of microglial function.[5] Previous studies in animal models have shown that microglial activation is necessary for POCD to occur[6] and also that Kv1.3 channels are required for microglial activation.[5] On the basis of these findings, Lai and colleagues[3] hypothesised that blocking Kv1.3 channels would prevent the activation of microglia and thereby mitigate POCD.

To test their hypothesis, the authors first studied the effectiveness of a small compound that inhibits Kv1.3 channels (phenoxyalkoxypsoralen-1 or PAP-1) in preventing POCD using a well-established mouse model of orthopaedic surgery. Briefly, healthy mice underwent a sham surgical procedure or repair of a tibial fracture under isoflurane general anaesthesia. Some mice were treated with PAP-1 by intraperitoneal injection before the surgery. Hippocampal-dependent memory

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