Scottish Airway Pioneers and Historical Accuracy

To the Editor:

In Dr. Bause's editorial in the February 2016 issue of Anesthesiology,[1] he very appropriately draws attention to the issue's admirable historical review from Dr. Matioc, concerning "airway command" for the years 1700 to 1846.[2] The editorial refers to "Scotland's Tossach, Fothergill, and Buchan."[1] While both William Tossach (b. prob. Perthshire, c.1700, d. Alloa, after 1771) and William Buchan (b. Ancrum, 1729, buried Westminster Abbey, 1805) were certainly born in Scotland, Dr. John Fothergill, a Yorkshireman (b. Carr End, 1712, d. 1780) was not. I made this same mistake in my article "History of mouth-to-mouth rescue breathing Part 2: the 18th century,"[3] which Dr. Matioc had kindly referenced (his Ref. 13). On learning of my error, I reported to the same journal's September issue[4] that I had come to consider John and Anthony Fothergill as Scotsmen "from their both attending the Edinburgh medical school and both being known as Northerners—but obviously they were not northern enough." After my article went to press, I learnt of John Fothergill's birthplace as Carr End[5] from the Oxford Dictionary of National Biography (DNB). Christopher Booth states of John Fothergill, "He studied medicine at Edinburgh because, as a Dissenter (he was a Quaker), he would be refused admission to universities such as Oxford."[5]

Finally, on returning after almost a decade to Part 3 of a mouth-to-mouth trilogy, I see I also had an instance therein of misnaming Anthony Fothergill (bap. 1737, d. 1813, and relation to John[5]) as "Andrew."[6(p224)] Apologies are offered for that further error.

Competing Interests

The author declares no competing interests.

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In Reply:

I thank Dr. Trubuhovich for reminding Anesthesiology's readership and me that the Doctors Fothergill were native Yorkshiremen and not Scotsmen. In preparing for my February 2016 editorial,[1] my files boasted a copy of Dr. Trubuhovich's[2] June 2006 article, but they lacked a copy of his September 2006 correction.[3] That is certainly my failing and not Dr. Trubuhovich's.

Competing Interests

The author declares no competing interests.

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Proof of Concept—How to Bridge Proof with Concept and Linked to Reality

To the Editor:

We read the article by Avramescu *et al.* published in Anesthesiology with great interest.[1] The authors investigated the effect of interleukin-1β on the γ-aminobutyric acid (GABA) inhibitory currents in hippocampal and cortical neurons after exposure to etomidate or isoflurane *in vitro*. They arrived at their findings with the use of a mice model of sepsis consisting of intraperitoneal lipopolysaccharide injection. They were able to show some interaction between lipopolysaccharide and some, not all, measures of behavioral effectiveness of two anesthetics. Overall, results described seem to offer insight on the potential relationship between inflammation and the amount of anesthetic needed

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in mouse models to achieve the desired anesthesia. In conclusion, the authors extrapolated the results of their study to clinically relevant scenarios of sepsis.

The authors picked one *in vitro* and one *in vivo* model of inflammation to test the effect lipopolysaccharide has on anesthetics mechanisms. *In vitro* part consisted of the stimulation of neurons with interleukin-1β at the concentration of 60 ng/ml determined to be an approximation of the cytokine environment in sepsis. But in sepsis, several cytokines are released concomitantly with interleukin-6 correlating the best with clinical outcomes. Moreover, the production of interleukin-1β by leukocytes stimulated by lipopolysaccharide can be significantly suppressed.[2] The concentration of interleukin-1β in serum or cerebrospinal fluid is not known despite an excellent opportunity presented by the *in vitro* part of the study. Furthermore, the presented article examines single exposure to interleukin-1β. This may be true for surgical procedures but not for the clinical scenarios with sustained and repetitive exposure to insulting agents like lipopolysaccharide and other pathogen mediators.

There is a long tradition of the study of inflammatory processes, most notably sepsis, and seemingly clinically relevant animal models. However, it has been almost uniformly shown that animal models consistently fail to mimic the immunologic environment as seen in human victims of septic shock.[3] This is frequently cited as one of the reasons for repetitive failures in translation of clinical drugs from animal platforms into the clinical realm.[4] Out of several available models (cecal ligation and puncture, interperitoneal bacteria injection), intraperitoneal lipopolysaccharide injections are especially very distant from clinical reality.[5] The dose of lipopolysaccharide was chosen to induce systemic inflammation with increase of interleukin-1β while preserving hemodynamic stability. This lack of measuring the hemodynamic changes induced by lipopolysaccharide injections prohibits accurate studying of this effect. Measuring serum interleukin-6 in sepsis has been shown to correlate with the magnitude of inflammatory response and mortality.[6] Therefore, measuring serum interleukin-6 and endotoxemia together is of particular importance since lipopolysaccharide itself can cause behavioral changes. This would help to address the question whether behavioral changes are related to systemic hemodynamically oriented changes *versus* generalized inflammation *versus* central neuroinflammation.

The choice of the anesthetic was dictated by selectivity for GABA receptor (etomidate) and popularity for use (isoflurane). However, the use of etomidate has decreased in sepsis and other systemic inflammatory response syndrome conditions because of the potential for adrenal suppression and associated mortality.[7] Etomidate does provide superb hemodynamic stability, but in this particular situation, the dose of lipopolysaccharide was chosen for its ability to keep hemodynamic stability and avoidance of profound septic shock, so it is unclear whether etomidate would be an appropriate agent in such clinical scenarios. Along with being as popular an agent as isoflurane, propofol has the intriguing benefit of certain immunomodulatory properties. For example, an article published in the same issue of Anesthesiology showed the positive effects of total intravenous anesthesia and cancer recurrence,[8] but it was not chosen by Avramescu *et al.*[1] Along with being frequently recommended as an appropriate agent to induce anesthesia in septic patients, ketamine has been shown to decrease interleukin-1β levels in the hippocampus.[9] Yet neither of these drugs were included in the study.

Furthermore, this article reports that although lipopolysaccharide did potentiate the immobilizing properties of etomidate, it did not do the same for isoflurane. This highlights the fact that the effect anesthetics have on the cerebral cortex and surrounding neurologic areas cannot solely be attributed to their action at GABA receptors. Similarly, their effects on the immune system are much more complex.

I applaud the investigators and authors on a well-designed experiment and a thorough, concise article. The results described seem to offer insight on the potential relationship between inflammation and the amount of anesthetic needed in mouse models to achieve the desired anesthesia. However, these results cannot be translated into clinical practice considering multiple obstacles in interpreting the results presented in the article in context of clinical context. In fact, altering the way clinical anesthesia is performed based on these results would not only be imprudent, but potentially detrimental to the patient.

Competing Interests

The authors declare no competing interests.

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In Reply:

We thank Dr. Laudanski for his thoughtful comments and questions. Our study[1] was motivated by the need to understand why critically ill patients, such as those in high inflammatory states (*e.g.*, due to sepsis, trauma, burns, autoimmune disease), are often more sensitive to general anesthetic drugs than are healthier patients. Identifying the factors that cause a standard dose of anesthetic to produce deeper levels of sedation in sicker patients is fundamentally important because of the risks associated with a relative drug overdose.[2] Indeed, excessively deep anesthesia may increase postoperative mortality.[3–5]

Clinical trials are underway to determine whether anesthetic dosing can be safely reduced in high-risk patients; however, discerning the specific factors that modify anesthetic sensitivity in patients is often problematic (see www.anzctr.org.au—ACTRN12612000632897 and www.clinicaltrials.gov—NCT00998894). Consequently, to test specific hypotheses, we used preclinical mouse models, which allow good control over experimental variables. We studied whether inflammation increases anesthetic up-regulation of γ-aminobutyric acid type A ($GABA_A$) receptor activity in neurons *in vitro*. Next, we tested whether such up-regulation correlates with the enhanced sensitivity for anesthetic behavioral endpoints induced by inflammation *in vivo*.[1]

Inflammation *in vitro* was mimicked by treating hippocampal and cortical neurons with a proinflammatory cytokine, interleukin-1β. As Dr. Laudanski correctly points out, inflammation stimulates the production of an array of cytokines, including interleukin-1β, interleukin-6, and tumor necrosis factor α.[6] We selected interleukin-1β for several reasons. An increase in interleukin-1β levels occurs in a variety of medical and surgical disorders, such as cancer,[7] aging,[8] sepsis-associated encephalopathy,[9] and surgical trauma.[10] Increased levels of interleukin-1β correlate with cognitive deficits in humans[9] and laboratory animals[10,11] and may potentiate the cognitive depressive properties of anesthetics. Also, we have previously shown that interleukin-1β increases the cell-surface expression of α5 subunit–containing $GABA_A$ receptors in the hippocampus,[11] whereas interleukin-6 and tumor necrosis factor α do not.[11] These α5 subunit–containing $GABA_A$ receptors are highly sensitive to up-regulation by many anesthetics.[12] Thus, the choice of interleukin-1β for this study was both reasoned and appropriate. We found that pretreating neurons with interleukin-1β markedly increased anesthetic up-regulation of $GABA_A$ receptor function.

Similarly, we selected etomidate and isoflurane for these studies for specific reasons. Etomidate, the most $GABA_A$ receptor–selective anesthetic,[13] causes minimal hemodynamic effects, which limits the impact of pharmacokinetic factors. Isoflurane, on the other hand, is widely used in clinical practice and has been extensively studied in laboratory animals, so comparisons could be drawn between our results and published data.[14] Interestingly, we found that other g-aminobutyric acid–mediated (GABAergic) drugs, including propofol and midazolam, also cause greater up-regulation of $GABA_A$ receptor function in hippocampal neurons treated with interleukin-1β (unpublished observation). It is of future interest to determine whether inflammation also potentiates the effects of non-GABAergic anesthetics, including ketamine and nitrous oxide.

Next, we adopted a widely used *in vivo* model of systemic inflammation to probe whether increased levels of endogenous cytokines increase sensitivity to GABAergic anesthetics. Mice were treated with a low dose of lipopolysaccharide (125 μg/kg) that was sufficient to stimulate an increase in cytokines rather than to mimic sepsis. Such a low dose of lipopolysaccharide does not produce gross hemodynamic instability, as confirmed by studies using echocardiography in isoflurane-treated animals.[15] We did not feel compelled to replicate these studies. Our results showed that lipopolysaccharide-treated mice exhibited greater sensitivity to etomidate, as evidenced by the increased hypnotic and immobilizing effects. Lipopolysaccharide-treated mice were also more sensitive to isoflurane but only for behavioral endpoints mediated by $GABA_A$ receptors, such as hypnosis but not immobility. Thus, only the $GABA_A$ receptor–dependent behaviors were modified in this experimental model. These results show that future studies must measure more than just the immobilizing properties of anesthetics, because minimum anesthetic concentration (MAC) values (considered a gold-standard measure of anesthetic potency) may not correlate with the dose required for hypnosis.

It was suggested by Dr. Laudanski that we measure interleukin-1β levels in the lipopolysaccharide-treated mice. Increased levels of interleukin-1β and other cytokines in the plasma and cerebrospinal fluid of rodents treated with lipopolysaccharide have been reported by others.[16,17] Also, cytokines are both autocrine and paracrine cell-signaling factors,[18] and measuring circulating cytokine levels has limited value in advancing our understanding of drug actions at the level of neurons.[18] In fact, interleukin-1β levels in brain tissue under inflammatory conditions are often higher than those in plasma or cerebrospinal fluid.[19] Interleukin-1β is produced locally in the brain in response to endotoxins by a variety of interleukin-1β–producing cells, including macrophages, microglia,[20] and astrocytes.[17] Moreover, levels of interleukin-1β in the serum are maintained at lower levels because interleukin-1β binds to circulating proteins, such as α2-macroglobulin and complement.[19,21] It would