ANESTHESIOLOGY

Anesthesiology: Resetting Our Sights on Long-term Outcomes: The 2020 John W. Severinghaus Lecture on Translational Science

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ABSTRACT

Anesthesiologists have worked relentlessly to improve intraoperative anesthesia care. They are now well positioned to expand their horizons and address many of the longer-term adverse consequences of anesthesia and surgery. Perioperative neurocognitive disorders, chronic postoperative pain, and opioid misuse are not inevitable adverse outcomes; rather, they are preventable and treatable conditions that deserve attention. The author's research team has investigated why patients experience new cognitive deficits after anesthesia and surgery. Their animal studies have shown that anesthetic drugs trigger overactivity of "memory-blocking receptors" that persists after the drugs are eliminated, and they have discovered new strategies to preserve brain function by repurposing available drugs and developing novel therapeutics that inhibit these receptors. Clinical trials are in progress to examine the cognitive outcomes of such strategies. This work is just one example of how anesthesiologists are advancing science with the goal of improving the lives of patients.

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Thank you, Dr. Rosenblatt, for your kind introduction, and thank you to the American Society of Anesthesiologists (ASA) for this tremendous honor of presenting the 2020 John W. Severinghaus Lecture on Translational Science. I will begin with a few comments about Dr. John Severinghaus, whom I first met in the Rocky Mountains at Lake Louise, Alberta, Canada, when he was attending a conference on hypoxia and high-altitude physiology. In fact, it was his love of nature, his curiosity, and his interest in high-altitude physiology that motivated Dr. Severinghaus to develop the first carbon dioxide electrode and blood gas analyzer.[1] You can see examples of his blood gas analyzers in the Smithsonian Institution and the Wood Library-Museum of Anesthesiology at the ASA headquarters in Schaumburg, Illinois.

Our paths crossed again when I regularly visited the University of California, San Francisco to participate in grant-writing sessions. Those intense weekends were organized by Professor Edmond "Ted" Eger II, who was the second Severinghaus Lecturer.[2] In what the group fondly referred to as "Tedfests," Ted would gather together a diverse group of collaborators and investigators and crowd us in a classroom on Saturday mornings to brainstorm about the molecular basis of general anesthesia. It was great fun—Dr. Severinghaus was a regular participant, and he would sit at the front of the classroom, often asking the most challenging questions. So today, as we honor Dr. Severinghaus and look to our future, we will ask ourselves the following challenging question: How do we, as anesthesiologists, achieve our full potential?

I will start this lecture with my own answer to that question, and this is the main take-home message for you: We can achieve our full potential as anesthesiologists by resetting our focus on improving long-term outcomes that impact the lives of patients. In other words, we must continue to provide excellent acute perioperative care, but we must also understand and mitigate the long-term consequences of surgery, inflammation, and exposure to anesthetic and analgesic drugs. I know that the 54,000 members of the ASA are deeply committed to providing the highest quality and safest care. But to do so, we must extend our horizon beyond the immediate perioperative period to consider the patient's cognitive, emotional, and physical long-term well-being.

Why do we need to reset our focus on long-term outcomes? Let me begin with a personal story. About a year ago, I was walking in Boston's central park, the Boston Common, and happened upon a beautiful monument and fountain. I was surprised to see, carved into the face of the monument, this message: "In gratitude for the relief of human suffering by the inhaling of ether a citizen of Boston has erected this monument."

On another side, the monument read: "To commemorate that the inhaling of ether causes insensibility to pain. First proved to the world at the Mass. General Hospital in Boston, October A.D. MDCCCXLVI." On the third side was quoted the Book of Revelation in the Bible: "Neither shall there be any more pain."

This monument was erected by someone who recognized that ether was going to completely change the face of medicine. After thousands of years of reliance on alcohol,

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blunt trauma, and extracts from the mandrake plant, the effects of ether must have been astonishing. Looking at that monument, I felt a tremendous sense of pride, knowing that I was part of one of the greatest medical discoveries of all time. For a moment, I was reminded of the reasons I chose anesthesiology as my professional calling. You may also remember the first time you witnessed the powerful properties of general anesthetic drugs because at some point early in your career, you were so moved by their therapeutic potential that you accepted the tremendous responsibility and privilege of administering them safely to patients.

As I walked around the Boston Common, I smugly noticed that there were no statues commemorating cardiac surgery or orthopedics or even personalized medicine because, by comparison, those innovations were mere incremental advances. I was feeling good. But as I was returning to my hotel, I began to feel a sense of unease and disquiet, a "cognitive dissonance." It dawned on me that although I felt pride in the notion of administering powerful anesthetic drugs, I also realized that this romantic view was simplistic and outdated. I asked myself, "Am I clinging to old ideas, at the risk of not fulfilling my potential as a clinician? Am I allowing this comfortable notion to obstruct new ideas and professional responsibilities?" It struck me that anesthesiology has evolved to encompass far more than drugs and the single patient–physician relationship.

Although our focus on the immediate perioperative period is necessary, it is no longer sufficient. The next transformation within anesthesiology is to target long-term outcomes that will improve the lives of our patients. This transformation requires that we ask of ourselves, "What happens to my patients after they leave the operating room or the trauma bay or the intensive care unit (ICU)? How can we improve their cognitive and emotional states, their mobility, and their ability to socialize and be productive citizens?"

This transition to addressing long-term outcomes will require each of us to adopt a culture of "relentless innovation" whereby we welcome new scientific discoveries and technical advances and also welcome the changes within our departments that will be required to accommodate these discoveries. But being open to change is not always easy, because so often it is the uncomfortable scientific truths and disruptive technologies that substantially improve patient care.

By way of example, I will be presenting some results from my laboratory that have challenged my thinking about the long-term effects of anesthetic drugs on the brain. More specifically, I'll be focusing on neurocognitive disorders, because many of us—and most of our patients—consider our brains to be our most valuable asset. Also, preserving brain function is likely a topic that many of your patients are raising in preoperative clinics.

Despite today's focus on cognition, I'm well aware that there are other, equally compelling long-term problems for us to address, including chronic pain, opioid misuse, and post-ICU syndrome. These disorders should not be viewed as inevitable but rather as preventable or treatable. Also, we must consider the long-term consequences of not having access to high-quality care, even in highly resourced countries.[3,4] These topics are equally deserving of our attention, even if they are not covered in my lecture today.

We now understand that perioperative neurocognitive disorders occur in a surprisingly large number of surgical patients, with the disorders ranging from delirium to persistent cognitive decline.[5,6] Delirium is an acute confused state characterized by alteration of consciousness with deficits in attention.[7] Persistent cognitive decline refers to longer-term cognitive deficits that last for weeks to months after surgery.[5,8] These two disorders are likely related, with delirium either being simply a harbinger of a longer-term cognitive disorder or contributing causally to longer-term decline. Collectively, they constitute some of the most common longer-term postoperative complications. In fact, approximately 26% of patients will be experiencing a decline in cognitive performance at the time of their hospital discharge, and 10% will continue to show these deficits 3 months later.[8]

Understanding the causes of perioperative neurocognitive disorders and finding strategies to prevent them are important because these disorders are associated with poor long-term outcomes, including loss of independence, admission to long-term care, and even increased mortality.[9–11] They are also expensive and are associated with substantially increased costs of hospital care related to prolonged ICU and hospital stays.[9,12,13] For example, here in Toronto, within the University Health Network, the estimated cost of delirium to a single institution is more than $17 million per year.[12] In the United States, delirium is a multi-billion-dollar burden to healthcare systems.[9,13]

Cognitive disorders are also common in medical patients who survive their stay in the ICU. For example, neurocognitive disorders occur in approximately 70% of ICU survivors who have experienced sepsis and who have chronic critical illnesses.[14] A timely example is the cognitive impairment observed in patients infected with SARS-CoV-2 who were admitted to ICUs. Early studies from Wuhan, China, reported neurologic findings and altered levels of consciousness and confusion.[15] More recent studies showed that 69% of ICU patients with COVID-19 had neurologic symptoms, including agitation and confusion after they were weaned from the sedative and neuromuscular blocking drugs.[16] Fully 33% of patients continued to experience executive dysfunction, as they were inattentive and disoriented, and they could not follow verbal commands for a prolonged period after ICU discharge.[16]

Statistics like these seem to be just numbers, so let me share one patient's journey. This is a story about an 87-yr-old woman who underwent elective hip arthroplasty under propofol sedation and spinal anesthesia. From the

surgeon's perspective, the patient had an excellent recovery and was discharged home on postoperative day 3. But in reality, during her recovery, she could not remember any of her visitors for weeks and was unable to manage her physiotherapy or medications. These were unintended cognitive consequences, which eventually improved. This is the story of my mother. She eventually recovered her cognitive abilities and gave me permission to tell her story because she hoped the complications that she experienced would not happen to others.

The causes of perioperative neurocognitive disorders are undoubtedly multi-factorial, with inflammation being a major contributing factor.[5,6,17,18] But we must ask the question, "Do general anesthetic drugs also contribute to long-term changes in brain function, and if so, can these drug-induced deficits be prevented or reversed?" The very notion of anesthetic drugs causing long-term effects was hard for me to accept because for decades, I have practiced under the assumption that after an anesthetic drug is eliminated from the body, the brain returns to its baseline state. However, a number of studies, the first of which was conducted not by anesthesiologists but rather by psychiatrists, clearly refuted this fundamental assumption.[19]

An important series of studies, first published in the early 2000s, showed that a single low dose of ketamine causes persistent behavioral effects that last long after the drug's lifetime.[19–22] The primary endpoint in these studies was not anesthesia but rather an improvement in depressive symptoms in patients who were refractory to standard care. The effects developed within hours and lasted for up to several weeks. For example, Zarate *et al.*[19] showed that depression scores, measured using the Hamilton Depression Rating Scale, improved for up to a week after a single low dose of ketamine. Since those initial studies, the results have been replicated by many other researchers.[20–22]

The protracted timeline of ketamine effects made no sense, in light of my own studies. After finishing my residency training in anesthesia, I completed a Ph.D. in molecular pharmacology under the mentorship of Professor John MacDonald. The research focused on understanding the molecular mechanisms underlying the neurodepressive properties of ketamine and propofol. I spent months studying ketamine's effect on the drug's primary target, the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor.[23] Those studies refuted the prevailing notion that ketamine inhibited the NMDA receptors simply by occluding or blocking the open channel pore. We showed that ketamine, like all other anesthetic drugs, acts allosterically as it reduces receptor function by stabilizing a closed state of the ion channel. But the more important point for this discussion is that ketamine blockade of NMDA receptors and recovery from the inhibition occurs on a time scale of milliseconds. Others have shown that this brevity of action is also reflected in the shortness of ketamine's half-life in the plasma.[24] The long-term antidepressant effect of ketamine in patients was puzzling because it occurred on a time scale that was multiple orders of magnitude longer than the dwell time of ketamine on the receptor and the duration of ketamine in the plasma. The mechanisms underlying this antidepressant effect are still controversial and are the subject of intense investigation by many labs including mine.[25]

For me, the ketamine results were a game-changer. They showed that a single exposure to ketamine could reset the genomic instructions that govern brain function for a prolonged period. Initially, I thought that such persistent effects were unique to ketamine, which in itself is a rather odd drug in our anesthetic repertoire, given that it targets glutamate receptors. Surely, I thought, similar persistent changes do not occur with anesthetic drugs that target the γ-aminobutyric acid type A ($GABA_A$) receptors—the drugs we use every day in the operating room. But I was wrong about that, and I will explain why.

After finishing my Ph.D. studies, I established my own lab, with the goal of addressing centuries-old questions, such as how anesthetics work, what their adverse effects are, and how those side effects can be prevented or reversed. Our studies have focused on the $GABA_A$ receptors, the primary targets for most injectable and inhaled anesthetic drugs and benzodiazepines.[26] $GABA_A$ receptors are ion channels that are widely expressed on the surface of neurons, where they sense the major inhibitory neurotransmitter in the brain, GABA. Binding of GABA to these receptors triggers opening of the integral chloride ion channels, which in turn allows the negatively charged ions to enter mature cells. This influx of anions hyperpolarizes the cell membrane and reduces neuronal excitability.[27,28]

Since the 1980s, we have known that these receptors contain binding sites for a variety of anesthetic drugs that increase the ability of GABA to activate ion channel opening and reduce neuronal excitability, thereby causing profound neurodepressive effects. These so-called GABAergic drugs include the volatile anesthetics isoflurane and sevoflurane and the injectable anesthetic drugs propofol and etomidate, as well as the benzodiazepines.[26–28] We have also learned that there are at least 19 different genes encoding the subunits that form pentameric protein complexes. The various subunit combinations confer different physiologic and pharmacologic properties. These receptors are ubiquitous and participate in many physiologic processes. Dysregulation due to alterations in either the number or the function of $GABA_A$ receptors contributes to a variety of disorders, including epilepsy, autism, depression, and neurodegenerative disorders. New drugs are currently being developed that target subpopulations of the $GABA_A$ receptors.[27,28]

Conventionally, we think that anesthetic drugs targeting $GABA_A$ receptors change receptor function on a time scale of milliseconds to seconds. For example, these drugs potentiate $GABA_A$ receptor–mediated currents that were recorded in mouse neurons. The effect is rapidly reversed in seconds after drug washout.[29] How could such rapid actions

contribute to long-term adverse effects that last for days or even longer?

For more than 20 yr, we have known that laboratory animals, particularly older animals that have been treated with commonly used GABAergic anesthetic drugs, exhibit deficits in cognitive performance that last long after the drugs have been eliminated.[30–34] For example, Culley *et al.*[30] studied the performance of 18-month-old rats that were trained in the radial arm maze. This task relies on spatial and working memory as the rats try to learn and recall the location of food rewards in the multiple arms of the maze. The rats in Dr. Culley's study were randomized to either an anesthesia group, which was treated for 2 h with a mixture of 1.2% isoflurane, 70% nitrous oxide, and 30% oxygen, or a control group, which received 30% oxygen. The rats were allowed to recover for 24 h and then were tested over the next 8 weeks. Over the testing period, the control rats got better at the task, as indicated by the shorter latencies to complete the maze. The anesthetized rats failed to improve with repeated testing.

It is important to highlight that postanesthetic deficits in laboratory animals are often subtle and are only evident in certain cognitive domains, which suggests that anesthetic drugs cause long-term changes in only certain vulnerable regions of the brain.[35] Also, even when deficits are present, they are not always or consistently detected in studies, which has led to some controversies and inconsistent results in this field.[17,36] We too have conducted a series of studies demonstrating cognitive deficits after exposure to both injectable and inhaled anesthetic drugs. These results were surprising to us, because we initially doubted that we would see deficits after the drug had been eliminated from the body.

We asked ourselves, what are the molecular mechanisms that contribute to these deficits? To answer this question, we turned to mouse models and three complementary experimental methods.

- Behavioral assays were used to test various aspects of cognition, focusing mostly on learning and memory.
- Electrophysiologic recordings were used to study the function of $GABA_A$ receptors. The microscopic currents generated by ions fluxing across the channels can be measured with voltage-clamp techniques and can be used as a read-out of receptor function. In fact, these microscopic currents are the primary way in which neurons communicate with each other.
- Biochemical approaches were used to measure changes in the number of receptors, as evidenced by changes in protein levels.

An example of one of our earlier studies, in which we studied the effect of 1 h of anesthesia with isoflurane or etomidate on memory behaviors measured 24 h later, is shown in figure 1.[33] We first tested whether the anesthetics caused deficits using a nonaversive paradigm of the novel object recognition test.[37] This test relies on a mouse's innate interest in novel objects. Mice, similar to humans, like novelty and will gravitate toward unfamiliar objects. The test involves placing a mouse in an arena and then allowing it to interact and become familiar with two identical objects. The mouse is then removed from the arena. One of the familiar objects is replaced with a novel object, and then the mouse is returned to the arena. If the mouse recognizes the novel object, it will spend more time interacting with the novel rather than the familiar object. Conversely, if it does not recognize the new object as novel, it will spend equal time with both objects. These relative interaction times can be used as a surrogate measure of memory. We can couple this test with preconditioning, by exposing the mice to a dose of anesthetic. Note that the drug has been eliminated from the mouse's body at the time of behavioral testing.

Control mice spent more time with the novel object as expected, whereas mice treated with isoflurane 24 h earlier did not. Similar results were obtained with animals treated with sevoflurane. We can also present the interaction times in terms of the so-called discrimination ratio, which is calculated as the interaction time with the novel object divided by the total interaction time with both the novel and familiar objects. A ratio greater than 0.5 suggests that the mouse recognizes the new object as novel (and spends more time with it), whereas the mice that don't remember the earlier training spend equal time with the two objects.

These studies were repeated with etomidate, and we saw similar results.[34] In fact, for many of our drug studies, we use etomidate. Although this drug isn't widely used in the clinical setting, it is highly suitable for our animal studies because it has a rapid onset of action, it targets $GABA_A$ receptors, it is rapidly metabolized without active metabolites, and it does not cause cardiorespiratory depression, which could confound our studies.[38,39] We found that etomidate caused subtle deficits up to 72 h after a single dose. The mice recovered by 1 week.

Why were the mice showing these memory deficits? To answer this question, we anesthetized the mice and allowed them to recover. We then isolated their brains and recorded $GABA_A$ receptor currents from neurons in hippocampal slices, because we hypothesized that there was a lingering increase in $GABA_A$ receptor function as shown in figure 2. We confirmed that $GABA_A$ receptor currents were indeed increased.[34] This increase after a single dose of etomidate persisted for 1 week. Finally, we found that this increase in current was due to an increase in the number of receptors expressed on the surface, as shown by cell-surface biotinylation. As such, this was not the allosteric increase in receptor function but rather an increase in *the number* of receptors on the cell surface that was causing the increase in current.

When we looked more closely, we discovered that only a certain subpopulation of $GABA_A$ receptors were overexpressed—those containing the $\alpha 5$ subunit ($\alpha 5$-$GABA_A$). These receptors are known to be crucially involved in

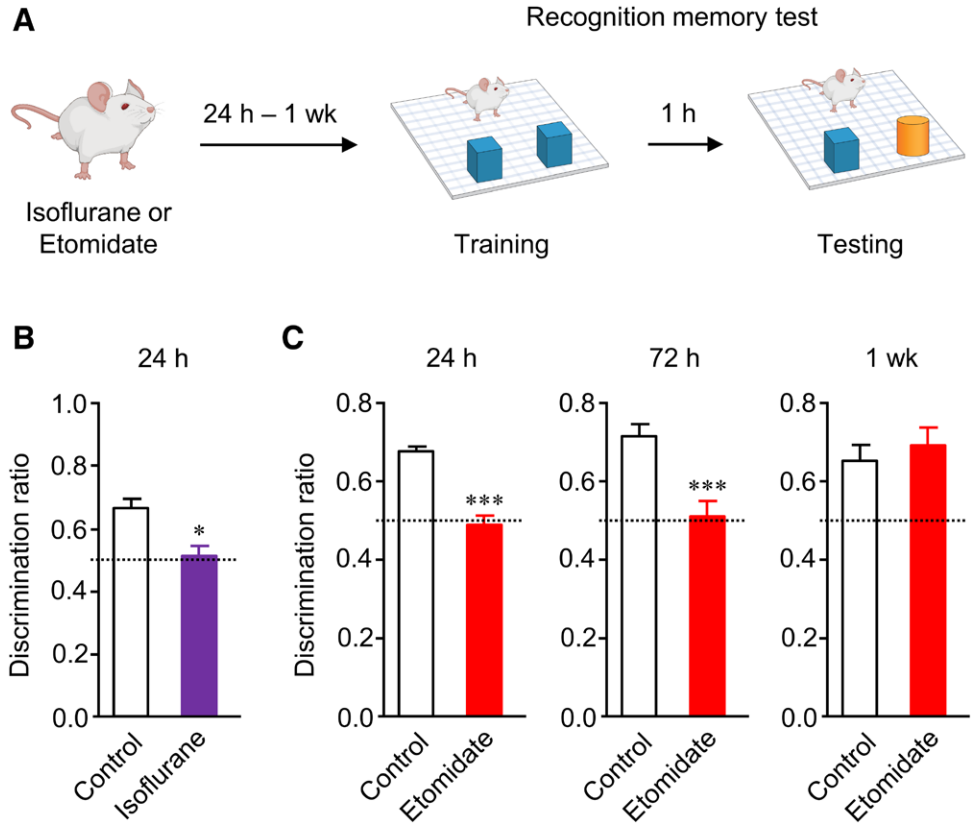

Fig. 1. Cognitive deficits after general anesthesia: A brief exposure to a general anesthetic drug causes persistent cognitive impairment. (*A*) The schematic illustrates the timeline and novel object recognition memory assay. (*B*) The discrimination ratio (time spent with novel object/time spent with both objects) is significantly lower in isoflurane-treated mice than control mice. n = 31, $^{*}P < 0.001$. Reproduced with permission from Zurek *et al.*[33] (*C*) Recognition memory is impaired up to 72 h after etomidate injection (8 mg/kg intraperitoneally). n = 9 to 12, $^{***}P < 0.001$. The *dotted lines* represent the chance level of interaction with the novel object (discrimination ratio = 0.5). Data are shown as mean ± SEM. Reproduced with permission from Zurek *et al.*[34]

memory processes.[40–43] In the lab, we affectionately refer to this type of receptor as the "stupid" receptor because we and others have shown that an increase in either its number or its function causes profound learning and memory deficits.[31,33,34,43–49] Importantly, when the anesthetic-treated, memory-impaired mice were treated with a drug that preferentially inhibits α5-$GABA_A$ receptors, memory performance was improved (fig. 3A). We also discovered that genetically modified mice lacking the α5-$GABA_A$ receptors did not show long-term cognitive deficits.[34] These results were exciting because they suggested a new "druggable" target for the treatment of perioperative neurocognitive disorders.

For this discovery of a class of drugs that could be used to reverse postanesthetic memory loss, the University of Toronto has been awarded several patents.[50–52] In fact, these drugs are now being developed by academic groups both small and large and by private pharmaceutical companies for other memory-enhancing purposes. As these drugs become available, we have examined their properties in the lab and plan to study their efficacy in surgical patients.[53] One drug in this class has been shown, in a small human trial, to be effective in reversing ethanol-induced memory deficits.[54,55] As a whole, this group of drugs has a good safety profile, likely because the receptor has a restricted distribution pattern.[46]

The next important observation was that not only did anesthetic drugs trigger excess surface expression of the "stupid" receptors, but also inflammatory factors produced similar overexpression of α5-$GABA_A$ receptors. More specifically, the proinflammatory factor interleukin 1β, which is elevated in critical illnesses, autoimmune disorders, and sepsis, increases cell-surface expression of α5-$GABA_A$ receptors.[48] In fact, levels of interleukin 1β have been correlated with cognitive deficits in patients with sepsis, as well as with delirium in patients with hip fracture.[56,57] Interleukin 1β increased the cell-surface expression of $GABA_A$ receptors, and these changes were associated with deficits in memory

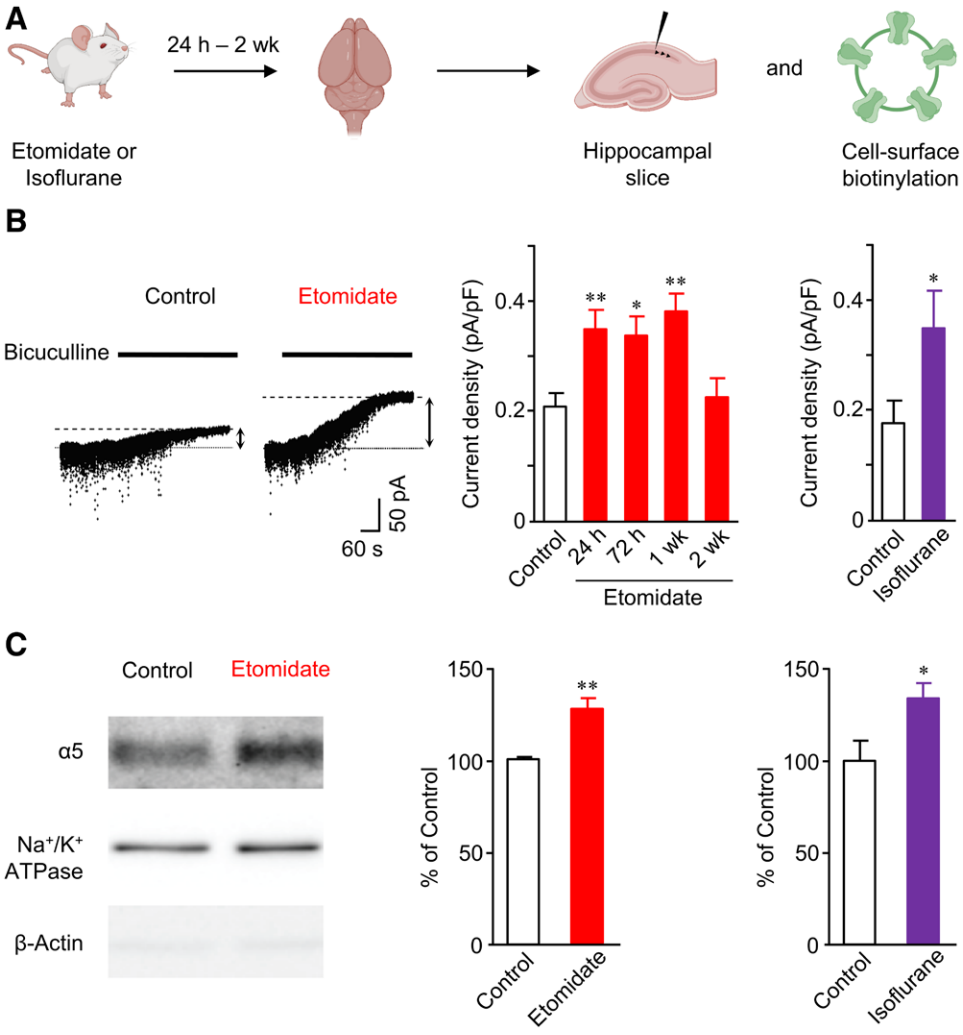

Fig. 2. The mechanisms underlying cognitive deficits after general anesthesia: A brief exposure to a general anesthetic drug causes a persistent increase in tonic current mediated by γ-aminobutyric acid type A ($GABA_A$) receptors and cell-surface expression of α5 subunits. (*A*) The schematic illustrates the timeline and experimental design. (*B*) Representative traces of tonic current recorded in a pyramidal neuron from hippocampal slices, and summarized data for 24 h to 2 weeks after etomidate injection (8 mg/kg intraperitoneally) or 24 h after isoflurane (1.3%, 1 h) are shown. n = 9 to 12, $^*P < 0.05$, $^{**}P < 0.01$ for etomidate; n = 9, $^*P < 0.05$ for isoflurane. (*C*) A sustained increase in cell-surface expression of α5 subunit 24 h after either etomidate injection or isoflurane treatment was observed. n = 6, $^{**}P < 0.01$ for etomidate; n = 6, $^*P < 0.05$ for isoflurane. Data are shown as mean ± SEM. Reproduced with permission from Zurek *et al.*[34]

performance. When we treated mice with interleukin 1β and with a drug that selectively inhibits the "stupid" receptor, we could attenuate memory deficits. Thus, drugs that inhibit α5-$GABA_A$ receptors may attenuate inflammation-induced memory deficits.[48]

We began to see an exciting convergence between drug-induced and inflammation-induced cognitive deficits, with the common downstream factor being excess activity of the α5-$GABA_A$ receptors. The next big question was, "What are the molecular mechanisms that trigger this excess expression of α5-$GABA_A$ receptors on the surface of neurons?" Experiments were designed to answer this question, and the results provided our next big surprise.

We first tried to reproduce the anesthetic-induced overexpression of $GABA_A$ receptors on the surface of neurons by treating isolated hippocampal neurons that were maintained in cell cultures with the anesthetic drugs, but our attempts utterly failed.[34] We expected to see an increase in the surface expression of receptors, as we had shown when we studied brain slices from anesthetic-treated mice. However, despite numerous attempts, we were unable to replicate our *ex vivo* findings. This setback was a big disappointment.

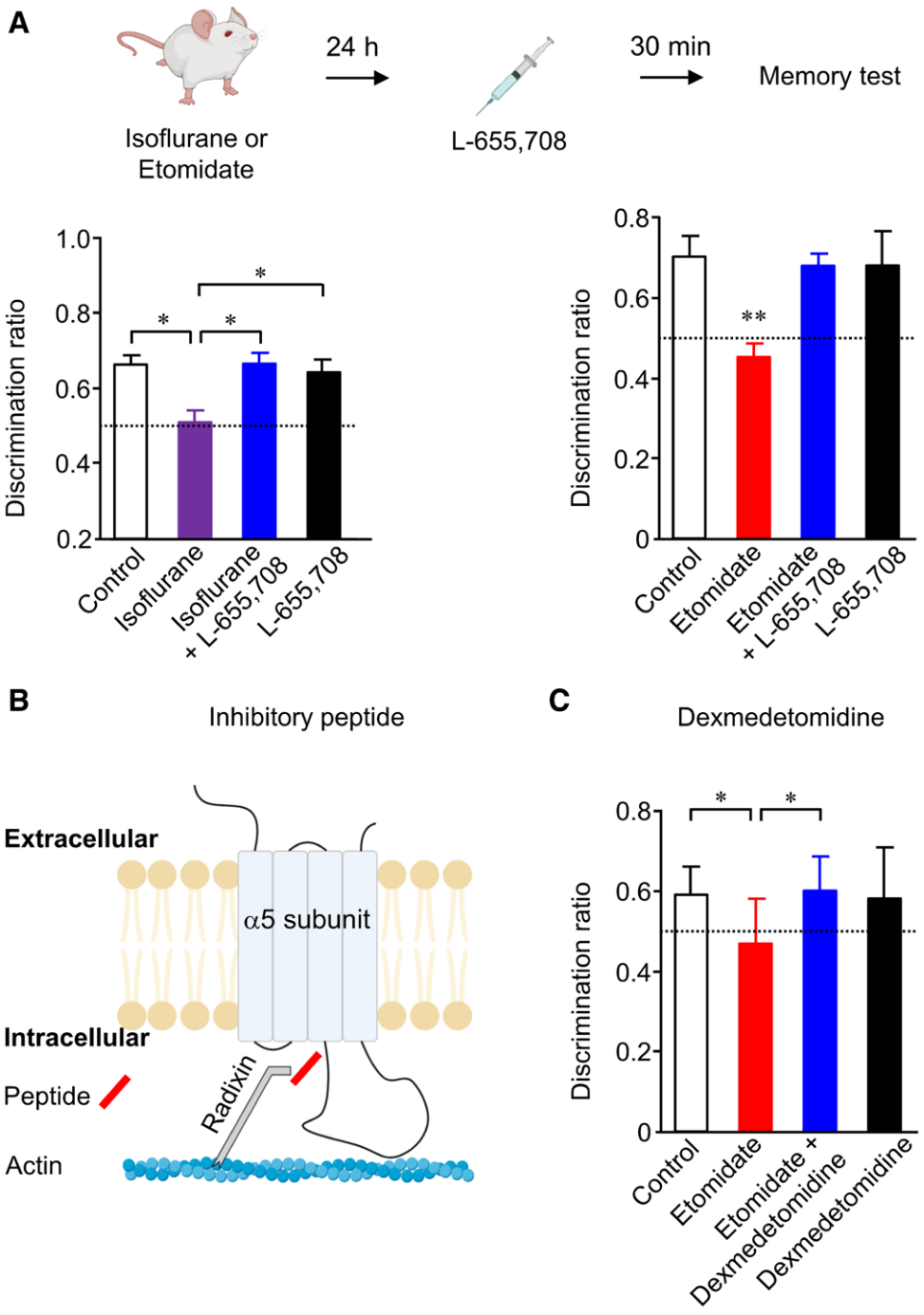

Fig. 3. Potential treatments for postanesthetic cognitive deficits: Strategies to mitigate persistent cognitive impairment after general anesthesia. (*A*) *Top*, A schematic of the timeline and experimental design. *Bottom*, Summarized data show that a negative allosteric modulator that inhibits α5 γ-aminobutyric acid type A ($GABA_A$) receptors (L-655,708) abolishes persistent memory deficits after either isoflurane or etomidate anesthesia. n = 31, 31, 11, 10 (left to right), $*P < 0.05$ for isoflurane; n = 6 to 11, $**P < 0.01$ for etomidate. Data are shown as mean ± SEM. (*B*) A schematic shows that a novel inhibitory peptide disrupts the binding of the anchoring protein radixin to α5 subunits and thereby prevents the excessive cell-surface expression of α5-$GABA_A$ receptors after anesthesia. (*C*) Dexmedetomidine prevents persistent memory deficits after etomidate anesthesia. n = 10, 12, 10, 13 (left to right), $*P < 0.05$. Data are shown as mean ± SD. The *dotted lines* represent the chance level of interaction with the novel object. Reproduced with permission from Zurek *et al.*[33,34] and Wang *et al.*[47]

We saw no increase in current in neurons that had been treated with anesthetic drugs. That's when a graduate student in our lab, Agnes Zurek, commented that neurons do not function alone. Rather, they are surrounded by glial cells, in particular astrocytes, which are the most abundant cell type in the brain. Nobel laureate Eric Kandel wrote, in his textbook *Principles of Neural Science*, that the ratio of glia to neurons is between 10 and 50 to 1.[58] Until recently, astrocytes have been thought to have a custodial or supportive role, with neurons being the center of attention. However, increasing evidence shows that astrocytes play critical roles in regulating physiologic processes and also contribute to pathology in the brain.[59]

Agnes proposed that we coculture the neurons with astrocytes, then treat the cultures with etomidate or sevoflurane. Sure enough, this approach triggered the overexpression of $GABA_A$ receptors that we had been expecting, as measured by the amplitude of GABA current, the same changes that we had observed in the *ex vivo* brain slices.[34] In fact, when we treated astrocytes on their own with either etomidate or a commonly used inhaled anesthetic drug, then harvested the supernatant from the cultures and applied it directly to the neurons, the culture medium alone was sufficient to stimulate the overexpression of $\alpha5$-$GABA_A$ receptors in the neurons. Thus, the astrocytes were releasing one or more soluble factors into the supernatant, and these factors were triggering the excess cell-surface expression of neuronal receptors.[34]

Our most recent results suggest that the astrocytes are releasing cytokines, possibly interleukin 1β. This particular cytokine plays a central role in the drug-induced overexpression of receptors, thus pointing again to a convergence between anesthetic-induced and inflammation-induced pathways, a convergence that is occurring on the $\alpha5$-$GABA_A$ receptors.

Armed with this new knowledge, we then asked, "How can we prevent or treat this overexpression of $\alpha5$-$GABA_A$ receptors and develop new treatments for perioperative neurocognitive disorders?" Earlier, I mentioned a class of drugs that preferentially inhibit $\alpha5$-$GABA_A$ receptors and noted that these drugs show some promise as treatments. However, in one study completed to date, the test drug failed to improve cognitive deficits associated with Down syndrome (http://www.clinicaltrials.gov; NCT02024789). Therefore, we have continued our search for new strategies.

Dr. Gang Lei, a postdoctoral fellow in our lab, had the next new idea. Rather than changing receptor function, perhaps we could target the machinery that keeps receptors stabilized on the surface of the neurons. The $GABA_A$ receptors are formed in the interior of the cell, and they need to be trafficked and maintained on the cell surface of neurons so they can sense GABA.[60] The $\alpha5$-$GABA_A$ receptor is the only subtype of $GABA_A$ receptor that interacts with the anchoring protein called radixin.[46,61–63] This protein links the receptors to the actin cytoskeleton and keeps them clustered, where they can sense low concentrations of extracellular GABA.

We took advantage of a unique protein–protein interaction, which relies on a set of several unique amino acids that contribute to the $\alpha5$-$GABA_A$ receptors, and we created an inhibitory peptide that mimics these interacting amino acids as shown in figure 3B. We modified the peptide so it could enter the cells by conjugating it to the amino acid sequence that confers cell permeability to the HIV virus. Our overall plan was to create a decoy that could disrupt the radixin-$GABA_A$ receptor interaction site. Preliminary results showed that it was possible to disrupt the excess cell-surface expression caused by the anesthetic drugs in cell cultures and also that pretreating mice with the inhibitory peptide improved cognitive performance after etomidate treatment. Of course, this peptide is not yet ready for "prime time," but the preliminary findings are exciting. The University of Toronto was recently granted a patent for this invention.[52]

We have also searched for more immediate, practical ways to reduce excess cell-surface expression of $\alpha5$-$GABA_A$ receptors. We asked whether there are drugs that can immediately be repurposed to prevent postanesthetic and inflammation-induced memory deficits. We knew from clinical studies that dexmedetomidine, an $\alpha2$ adrenergic receptor agonist, attenuates delirium in patients. For example, a study from the University of Toronto showed that after cardiac surgery, ICU patients sedated with dexmedetomidine for a 24-h period showed reduced incidence and duration of delirium, relative to those sedated with propofol.[12] Similarly, dexmedetomidine caused a remarkable reduction in delirium in patients who were treated in the ICU after noncardiac surgery.[64]

We next asked whether dexmedetomidine could prevent overexpression of the receptors. Dr. Dian-Shi Wang, a senior research associate in our lab, led this project, and this is what we discovered.[47] In behavioral studies, dexmedetomidine prevented the anesthetic-induced deficits in performance in the object recognition test with mice (fig. 3C). These results were particularly surprising, given that the mice cotreated with dexmedetomidine were sedated 30% longer than controls. Despite this prolongation in sedation and recovery, dexmedetomidine improved memory performance the next day.

We next asked, "Does cotreatment with dexmedetomidine prevent the increase in current generated by $GABA_A$ receptors in hippocampal neurons?" Studies of *ex vivo* brain slices showed that cotreatment with dexmedetomidine prevented the overexpression of receptors in the hippocampus.[47] Studies of cultured neurons and astrocytes provided further corroborating evidence; cotreatment with dexmedetomidine prevented the increase in current after etomidate treatment. Interestingly, we have learned that dexmedetomidine, just like etomidate, first acts on

astrocytes, not the neurons, to trigger these changes. Finally, we treated human astrocytes and found that dexmedetomidine stimulated these astrocytes to release factors that prevented the overactivity of $\alpha5$-$GABA_A$ receptors. In fact, dexmedetomidine was stimulating the release of a tropic or supportive factor known as brain-derived neurotrophic factor, which attenuated the increase in cell-surface expression of the "stupid" receptors in neurons. Thus, astrocytes were driving the show, with neurons serving as responders.

Overall, the results have provided convincing evidence that commonly used anesthetic drugs trigger sustained changes in the cell-surface expression of $GABA_A$ receptors, changes that persist long after the drugs have been eliminated from the body. Inflammation and drugs share common components in their signaling pathways and also share common downstream effectors, the $\alpha5$-$GABA_A$ receptors. Astrocytes, the most prevalent cells in the brain, are the primary targets, and these cells release soluble factors that both cause and prevent the changes in neurons.

So, what is the overall impact of our research? The impact of these findings is summarized:

- We identified mechanisms to account for anesthetic-induced and inflammation-induced cognitive deficits that occur in patients as mouse and human $\alpha5$-$GABA_A$ receptors show striking homology, with similar structural and functional properties.
- We identified a "druggable target" that, in the future, may be safely manipulated for restoring brain function. Drugs that target $\alpha5$-$GABA_A$ receptors have already been trialed for cognitive deficits and other disorders and have a good safety profile.
- The inhibitory peptide or decoy strategy is a new approach that can prevent the increase in cell-surface expression of $\alpha5$-$GABA_A$ receptors.
- A mechanism to account for the cognition-sparing properties of dexmedetomidine has been identified. The results also position astrocytes at the forefront to research that aims to understand the causes of perioperative neurocognitive disorders.
- From a practical perspective, the studies have stimulated others at my own hospital, Sunnybrook Health Sciences Center in Toronto, Canada, and possibly elsewhere to further develop screening and prevention programs to reduce the risk of postoperative delirium.

Finally, I have told my story today in the context of perioperative neurocognitive disorders; however, our lab and others have shown that excess activity of the $\alpha5$-$GABA_A$ receptors likely contributes to other disorders, including traumatic brain injury, depression, and neurodegenerative disorders such as Alzheimer disease.[65–70] As such, the lessons we have learned from studying anesthetics can likely be extended to these disorders as well.

I'd like to highlight one additional comment about how we can accelerate the translation of research findings into new treatments that improve the long-term outcome of patients. I already noted the importance of each of us to establishing a culture of "relentless innovation." The second, equally important factor required for us to achieve our full potential is to be very purposeful and mindful about the people with whom we work. We need to surround ourselves with colleagues and collaborators who can help with this transition. Just as Ted Eger did at the "Tedfests" of long ago, we need to attract diverse groups of collaborators and investigators to support our mission. We also need to train our young professionals, who must acquire the research and administrative skills that will allow them to integrate preclinical and clinical research into practice. Organizations such as the ASA play a vital part in fostering collaborations with other medical and scientific disciplines, and in training our future leaders.

We need to come together to actively support such organizations. In fact, the ASA has established a multidisciplinary team with a specific mandate to address perioperative neurocognitive disorders. You can learn more about this experienced group and their activities by visiting their website (https://www.asahq.org/brainhealthinitiative). Here at the University of Toronto, we have established the Perioperative Brain Health Center (http://www.perioperativebrainhealth.com). This center hosts a diverse group of investigators who have undertaken several clinical projects.

- Dexmedetomidine effects on long-term cognitive outcomes in noncardiac and cardiac patients are being studied by Steven Choi (http://www.clinicaltrials.gov; NCT04289142).
- Potential adverse effects of benzodiazepine on postoperative cognitive performance in cardiac patients are being studied by Jessica Spence (http://www.clinicaltrials.gov; NCT03928236).[71]
- The antidepressant properties of nitrous oxide on patients with bipolar disorder are being studied by Benjamin Goldstein (http://www.clinicaltrials.gov; NCT02351869).[72]

In summary, I hope I've convinced you that we must continue to celebrate our heritage without clinging to outdated and constraining conceptual models. We must keep an open mind and reset our focus on improving long-term outcomes that affect the lives of our patients. Long-term problems, including chronic pain, opioid misuse, and post-ICU syndrome, should not be viewed as inevitable but rather as preventable or treatable disorders. Preclinical studies will reveal the underlying pathophysiology and identify new treatments for these disorders.

We know that achieving these goals will not be easy. The sheer volume of clinical cases means that there are increasing demands on your time. But when faced with time demands and uphill battles, we can look to the namesake of this lecture for inspiration. Dr. Severinghaus was able to

continue providing clinical care even while he was developing practice-changing devices, participating in Tedfests, and fostering a contagious culture of "relentless innovation." His legacy for innovation lives on to this day at University of California, San Francisco.

Dr. Severinghaus can offer us one final lesson. He enjoyed the great outdoors and took many backpacking trips with his family. Perhaps you too have turned to nature to gain strength during the COVID-19 pandemic. I certainly have. My family likes canoe trips, and on one such trip during this strange past summer I was thinking about how we, as anesthesiologists, can circumvent the obstacles that thwart our goals. I found myself considering this question in paddling terms.

The first rule of paddling a canoe in rough waters is to focus—not on where you are, but on where you want to go. Be aware of the rocks and other hazards, but set your sights on your target, so that you will not be thrown off course. When navigating through the rapids, do not rush the descent. In fact, sometimes you will need to back-paddle (remembering that not all ideas are worth pursuing), and you may need to slow down so that you can see the next obstacles. But in the big waves, the best way to avoid capsizing is to paddle strongly forward. It is time for anesthesiologists to paddle strongly forward and achieve our full potential by focusing on the long-term outcomes of our patients, including the cognitive, emotional, and physical states that allow them to be happy and productive.

In closing, I again thank the ASA for the opportunity to share our research findings. I also thank the many talented trainees who contributed to the research that I have presented today and the funding organizations that have made this work possible. Most importantly, I thank my family for their continuing love and support, and I thank you for your attention.

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Competing Interests

Dr. Orser serves on the Board of Trustees of the International Anesthesia Research Society (San Francisco, California) and is a co-director of the Perioperative Brain Health Center (Toronto, Ontario, Canada; http://www.perioperativebrainhealth.com). She is a named inventor on a Canadian patent (2,852,978) and two U.S. patents (9,517,265 and 10,981,954). The new methods identified in the patents aim to prevent and treat delirium and persistent neurocognitive deficits after anesthesia and surgery, as well as to treat mood disorders. Dr. Orser collaborates on clinical studies that are supported by in-kind software donations from Cogstate Ltd. (USA).

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