ANESTHESIOLOGY

Musings from an Unlikely Clinician–Scientist

2018 American Society of Anesthesiologists Excellence in Research Award

Beverley A. Orser, M.D., Ph.D.

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ABSTRACT

This article, which stems from the 2018 American Society of Anesthesiologists Excellence in Research Award Lecture, aims to encourage young investigators, offer advice, and share several early life experiences that have influenced the author's career as an anesthesiologist and clinician–scientist. The article also describes key discoveries that have increased understanding of the role of γ-aminobutyric acid type A ($GABA_A$) receptors in health and disease. The author's research team identified the unique pharmacologic properties of extrasynaptic $GABA_A$ receptors and their role in the anesthetic state. The author's team also showed that extrasynaptic $GABA_A$ receptors expressed in neuronal and nonneuronal cells contribute to a variety of disorders and are novel drug targets. The author's overarching message is that young investigators must create their own unique narratives, train hard, be relentless in their studies and—most important—enjoy the journey of discovering new truths that will ultimately benefit patients.

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Last year, I had the honor of presenting the 2018 American Society of Anesthesiologists Excellence in Research Award Lecture. This article is based on that lecture and is framed around three questions: Why did I choose a career in anesthesiology? Why am I passionate about research? What have we discovered? It has been an exciting journey, and by sharing a few of my own stories, I hope to encourage and support young investigators, and explain some of our scientific findings that have identified extrasynaptic γ-aminobutyric acid type A ($GABA_A$) receptors as novel therapeutic targets.

Developing an Interest in Anesthesiology

We have all interacted with mentors who have deeply influenced our careers. That was the case for me in the summer of 1980 when I arrived at St. Jude Hospital in Saint Lucia, West Indies, as a final-year medical student. Three days earlier, Hurricane Allen, a class 5 storm, had ravaged the country, leaving six dead and many injured.

The only anesthesiologist working at St. Jude Hospital, Dr. Vincent Hughes, M.D., was stranded at the northern tip of the island. He could not travel south to where the hospital was located, because hydro wires and fallen trees were blocking the roads. At the hospital, the situation was grim: Many patients urgently needed surgery, but no anesthetic care was available.

Dr. Hughes managed to get back to the hospital several days later and immediately took charge. He personally cared for the sickest patients, organized the operating rooms, and helped to restore a sense of order. Observing Dr. Hughes's work left me with a lifelong impression about the immense need for safe anesthetic care and the importance of anesthesiologists as clinicians and team leaders.

After completing medical school and a rotating internship, I undertook a 6-month anesthesia course for family physicians and then headed to northern Canada to work in underresourced communities. The hospital was in Baie Verte, Newfoundland (49°93' N), a town with a population of about 1,300. The hospital served the fishing villages that dotted the north coast of the island. The clinical work was exciting and it sparked a lifelong interest in patient safety and the science of anesthesiology.[1–3] I soon wanted to focus my clinical practice on anesthesia and thus returned to an academic center in Ontario to complete residency training.

Becoming a Scientist

During my residency training, I worked with many exceptional mentors. However, the ones whom I admired most shared a common view that academic physicians have two jobs: the immediate task of caring for each patient and the longer-range task of building a better future for all patients either by generating new knowledge or by best utilizing existing resources.

The recognition of the two tasks leads me to my second question: Why am I passionate about research? Toward the end of residency training, I became more interested in the work of researchers for a simple reason: They seemed to be having the most fun, whether they were launching multicentered clinical trials or performing preclinical studies. I noticed that the top investigators shared several common admirable characteristics. They were relentless in their work habits, and they believed that their discoveries had the potential to improve the lives of millions. They were also

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remarkably resilient and were able to bounce back from repeated challenges and defeats. Dr. John M. Zerwas commented about this type of resiliency in his 2018 Emery A. Rovenstine Memorial Lecture. In his presentation entitled "Mentoring the Next Generation of Leader," he quoted a Japanese proverb: "Fall down seven, get up eight."

As suggested by the proverb, the successful investigators—the ones who were able to develop sustained research programs—were tenacious and able to pick themselves up after repeated rejection or failure.

Yet for me, a career as a clinician–scientist seemed highly unlikely as I thought that I lacked the necessary grit. In addition, in my family, there were few role models and certainly no scientists or physicians. Growing up in small-town Ontario, the only science journals to which we were exposed were the *How and Why* series of children's magazines. Even so, at age 10 yr, I asked for and received a toy microscope. However, the experiments performed in my basement were boring, and my interest in science waned, at least for a time. Further, I was not a particularly noteworthy high school student. In grade 8, we moved to a non-English community and I did not speak the language. It took considerable time for me to catch up academically to my peers.

While preparing for this talk, I discovered an even more important reason why research was an unlikely career choice for me. To understand this next point, you need to know that I am one of four girls—and an identical twin. While searching the internet to find photos of that first toy microscope in preparation for this talk, I discovered that *all* the young people depicted on the boxes of children's microscopes looked nothing like me —they were all boys. I found one image of a girl on a microscope box, but she was relegated to observing experiments from behind the "real" scientist. There was one science kit for girls, but it was for technicians. The implicit message was that someone who looked like me could perhaps contribute to research, but only as a technician, not as a scientist. As the old saying goes, "You can't be what you can't see." Biomedical research or even medicine was not in the realm of career possibilities until several years after I entered university. I have since learned that if you are passionate about the work, you will find the resolve and resources to overcome barriers.

Although inclusion and diversity in medicine and science have certainly improved in the intervening decades, I believe it is worthwhile to mention these experiences. As you build your careers, you may not see yourselves reflected in those around you. This means that you must be prepared to write your own unique narrative, one that does not depend on your gender, race, age, first language, or accent. We all know that the systems in which we work present barriers, but the greatest barriers are the ones we subconsciously internalize—the ones that lie within ourselves. To overcome these barriers, you will need to envision yourself in exciting new roles. Look for mentors who can help you and who will support that self-image. I was fortunate to have a supportive teacher in grade 12 who saw some potential in me and encouraged me to apply to universities and continue in science.

This brings me to an important point about mentors and advisors. Even after leading my own laboratory for more than 25 yr, I still reach out to mentors who support my research and leadership interests. I consider these advisors to be my "personal board of directors." They help me to solve problems expeditiously and avoid major pitfalls. In turn, I now serve as a mentor to others.

Evolving a Research Career

The question of how anesthetic drugs depress brain function had intrigued me since my time working in Newfoundland. Consequently, after residency training, I undertook doctoral studies with the late Dr. John F. MacDonald. The studies focused on $GABA_A$ receptors, which mediate the majority of inhibitory neurotransmission in the brain.[4,5] γ-Aminobutyric acid (GABA), the major neurotransmitter, binds to the receptor and triggers the opening of an integral anion channel; the resulting influx of anions hyperpolarizes the neurons and reduces excitability. Most anesthetic drugs bind to $GABA_A$ receptors and potentiate the opening of the anion channel.[6,7] We discovered that one of these drugs, propofol, increases the function of $GABA_A$ receptors by three different mechanisms: increasing the potency of GABA, directly opening the ion channel, and preventing the receptors from entering a closed or desensitized state.[8]

When I established my own research lab, I asked questions more related to my clinical practice. We focused on three mysteries that have perplexed scientists for centuries: How do anesthetic drugs work? What are their side effects? Can we prevent these side effects? Specifically, we wondered how anesthetic-induced changes in $GABA_A$ receptor function cause behavioral changes *in vivo*. We knew that anesthetic drugs cause multiple behavioral effects, including memory loss, unconsciousness, pain relief, and immobility.[9] In particular, we wanted to understand the basis of the memory blocking or amnestic properties of anesthetic drugs for several reasons. First, amnesia is one of the most potent and essential properties of anesthetic drugs.[10] Second, we used the anesthetic drugs as pharmacologic probes to understand the underpinnings of memory processes. Finally, we sought insights into memory dysregulation that could have broad impacts beyond the field of anesthesiology.

We now understand that there are two distinct forms of anesthetic-induced memory loss. The first is the acute, profound amnesia that occurs when an adequate concentration of the anesthetic drug is present in the brain. The second is a much subtler memory deficit that occurs long after the drugs have been eliminated. This form of memory loss is not readily apparent and lasts longer than the lifetime of the drug.[11]

Our initial experiments aimed to identify subpopulations of $GABA_A$ receptors that mediated the acute and

profound anesthetic-induced memory loss. We already knew that multiple genes encode the subunits forming $GABA_A$ receptors, and that the pharmacologic properties of receptors differ according to the subunit composition.[4,5] We tried to find "super-sensors"—$GABA_A$ receptors that were sensitive to low, memory-blocking concentrations of several anesthetic drugs—so we searched for these receptors in a brain region that is critically involved in memory, the hippocampus.

$GABA_A$ receptors cluster at synapses, the contact points between neurons. GABA released in packets or quanta activates postsynaptic $GABA_A$ receptors, which generate fast, transient postsynaptic currents. These fast transient currents allow brain cells to communicate with each other on a rapid millisecond timescale.[4,5]

We initially postulated that low, memory-blocking concentrations of anesthetics would potentiate a subpopulation of postsynaptic inhibitory currents. Using electrophysiologic recordings, we searched for synaptic currents that were prolonged by low concentrations of propofol in hippocampal neurons. However, we failed miserably in that attempt, because our recordings were repeatedly contaminated by an annoying noise or low-amplitude current that reduced the recording quality. This "artifact" kept recurring, and we kept discarding these "contaminated" recordings, until one day, the penny dropped. What we had been mistakenly treating as an artifact was in fact the anesthetic-evoked inhibitory current we were looking for. Surprisingly, it was not mediated by synaptic receptors; rather, it was a novel tonic or persistent current generated by a different subtype of $GABA_A$ receptor.[12]

Further, when we applied nonselective blockers of $GABA_A$ receptors, we observed two important changes.[12] First, as expected, the blocker eliminated the transient synaptic current, but it also shifted the baseline current. This baseline shift occurred because the blocker was unmasking a novel tonic current. In other words, the anesthetic drug increased the current, causing an inward shift, whereas the blocker inhibited the current causing an outward shift. More important, we observed that low concentrations of several anesthetic drugs caused a multiple-fold greater increase in tonic current than the synaptic current. We now appreciated that $GABA_A$ receptors that generate the tonic current are critically important and selective drug targets. We have also since learned that under baseline conditions, these receptors regulate memory processes.[13–17] In this context, the anesthetic drugs were indeed effective probes that offered valuable insights into the physiology of memory processes.

We next postulated that the tonic current was generated by distinct populations of extrasynaptic $GABA_A$ receptors. A postdoctoral fellow working in the laboratory, Dr. Donglin Bai, made a serendipitous discovery that was the first step to confirming this hypothesis.[12] He identified a specific antagonist that preferentially inhibited the synaptic current but not tonic current. In contrast, nonselective antagonists blocked both the synaptic and the tonic currents. Subsequently, using molecular techniques, we showed that $GABA_A$ receptors exhibiting anesthetic "super-sensor" properties are indeed unique. Different genes produce subunits that form extrasynaptic receptors, and they often contain $\alpha5$ subunits.[18,19] Notably, genetically engineered mice that lacked $\alpha5$ subunit-containing $GABA_A$ receptors were resistant to the memory-blocking properties of an anesthetic drug.[14–17] The $\alpha5$ subunit-containing $GABA_A$ receptors normally contribute to physiologic memory processes, and anesthetic drugs "highjack" their memory-blocking properties and cause profound amnesia.

Thus, the conceptual model of $GABA_A$ receptor-mediated inhibition evolved. We have since learned that these extrasynaptic $GABA_A$ receptors play unique roles in many physiologic and pathologic processes including learning and memory, pain, asthma, and insulin secretion.[5,10,20–22]

Beyond exploring the mechanisms of action of anesthetic drugs, we have also been investigating the side effects of general anesthetic drugs. Over the years, several research teams have shown that exposure to anesthetics induces a subtle "fog" that impairs neurobehavioral functions after the drugs have been eliminated.[23–25] Understanding the molecular basis of this brain fog is important, as it may contribute to adverse events we observe in patients, such as delirium and other postoperative neurocognitive disorders.[26]

Studies undertaken with the goal of identifying the molecular basis of the brain fog led to an unexpected discovery. Graduate students Bechara Saab and Agnieszka Zurek confirmed that exposure to anesthetics triggered subtle memory deficits that persisted after elimination of the drugs.[27–29] One study, using an object recognition assay, illustrates this point.[28,29] This particular assay depends on the subjects' innate preference for novelty. When a mouse is placed in a novel context that contains two objects, it explores around and interacts with the two objects. The mouse is then taken away from the context for a few minutes, during which time one of the now-familiar objects is replaced with a new object. When the mouse is returned to the context, it recognizes the remaining familiar object, but it tends to gravitate toward and interact with the novel object. The time spent interacting with the novel object is used as a surrogate measure of memory. This memory assay can be coupled with drug treatments to probe long-term memory deficits.

In our studies, we observed that mice treated with vehicle spent more time with the novel object, as expected, whereas mice that had been anesthetized 1 to 3 days earlier exhibited no preference for the novel object.[29] These mice behaved normally in all other respects, but exhibited what we call a preference deficit.

Surprisingly, treating the mice with a drug that blocked the $\alpha5$ subunit-containing $GABA_A$ receptors restored memory performance.[28,29] These findings suggested to us that the brain fog resulted from overactivity of memory-blocking

α5 subunit-containing $GABA_A$ receptors. Importantly, genetically modified mice lacking α5 subunit-containing $GABA_A$ receptors never exhibited such memory deficits after general anesthesia. Thus, extrasynaptic $GABA_A$ receptors contribute to the profound, desired memory loss that occurs during anesthesia, but they also contribute to undesired, persistent memory loss that lasts long after the lifetime of the drugs.

Our third area of inquiry aimed to determine how these adverse effects could be prevented. These studies are important because the results might provide clues for treatments of delirium and postoperative neurocognitive disorders. We reasoned that if overexpression of "stupid" receptors contributes to persistent cognitive deficits after general anesthesia, then inhibiting them should help to restore function.

We studied several strategies to reduce the overactivity of α5 subunit-containing $GABA_A$ receptors. First, we showed that negative allosteric modulators of α5 subunit-containing $GABA_A$ receptors can restore persistent memory loss after general anesthesia in mice.[28–30] For this discovery, the University of Toronto, Toronto, Canada, has received several patents for the treatment of postoperative cognitive deficits. Second, we knew that α5 subunit-containing $GABA_A$ receptors form inside the cells and must be trafficked to the cell surface before they can respond to GABA. Therefore, we developed an inhibitory peptide that enters the cell and prevents the overexpression of receptors on the cell surface. This inhibitory peptide prevents postanesthetic memory deficits, at least in animal models; a U.S. patent is pending for this discovery.

Finally, we have been studying dexmedetomidine, the only available drug that prevents postoperative delirium.[11,31,32] In this work, we have used a reverse translation approach to determine whether dexmedetomidine modifies the activity of α5 subunit-containing $GABA_A$ receptors. Our thinking goes like this: If overexpression of α5 subunit-containing $GABA_A$ receptors underlies delirium, and if dexmedetomidine prevents delirium, then dexmedetomidine should prevent the overexpression of α5 subunit-containing $GABA_A$ receptors. Dr. Dian-Shi Wang, a senior research associate in my laboratory, has shown that dexmedetomidine triggers the release of brain-derived neurotrophic factor, and possibly other soluble factors that prevent the anesthetic-induced overexpression of α5 subunit-containing $GABA_A$ receptors.[11,31] For those interested, Anesthesiology produced an excellent video that is available at https://youtube/aZ2Uq2rwtiw (accessed June 25, 2019).

Finally, others showed that overexpression of extrasynaptic $GABA_A$ receptors occurs in other disorders, including depression and stroke.[30,33,34] Strategies that we identified through our studies of anesthetic mechanisms may be helpful in addressing disorders beyond the field of anesthesiology.

Our future studies will examine the clinical effectiveness of these treatments. To undertake the necessary clinical studies, we established the Perioperative Brain Health Centre in Toronto, Canada (http://perioperativebrainhealth.com; accessed June 25, 2019). We have also worked with the American Society of Anesthesiologists to develop strategies to preserve cognition. Exciting studies lie ahead.

Parting Advice

In closing, I will leave you with several words of advice. First, I would emphasize that the most important thing you can do early in your career is to train hard. If you are serious about a career in research, I encourage you to consider graduate school training. Second, work with the best mentors you can find, and observe your mentors carefully. Good research habits formed in the early years will propel your career forward.

Some of you might be wondering, what is the best topic to study? Here, I'm stumped because we never had a master plan but simply followed the path as it led from one interesting study to the next. From our perspective, the choices were simple. We asked ourselves, "What is the coolest, most compelling experiment we can design?" Then, once we had launched a project, we constantly asked ourselves, "Are we doing the *right* experiment, as opposed to the *easiest* experiment? Are we stuck in a rut, afraid to pivot or even completely change direction, when the science demands such changes?"

These experiences lead me to my final five take-home messages:

- Focus on your data, and you will find that the results have a life of their own. If you sit quietly, study, and concentrate, your data will reveal marvellous new stories.
- If the data do not fit your hypothesis, great! It is likely because your hypothesis is wrong, and the data will help you to discover where the errors lie.
- Constantly check your assumptions and biases. These potential pitfalls are dangerous because they can take you down dead-end paths.
- Don't dither—just do the experiment. That said, good scientific outcomes follow from good planning. Attention to details and rigor in execution are essential.
- Finally, a tip for more senior investigators: we all work best in diverse teams. Surround yourself with a diverse group of people and support them in your work together.

I hope that I've answered the three questions posed at the beginning of my talk: Why did I choose a career in anesthesiology? Why am I passionate about research? What have we discovered?

As anesthesiologists, you have selected an incredibly exciting field of medicine. Your career path may not always seem clear, and you may not see yourself reflected in the leaders you want to emulate, but as Charles Pierce suggested,

> There is one thing even more vital to science than intelligent methods; and that is, the sincere desire to find out the truth, whatever it may be.

In your quest to find out the truth, whatever it may be, I encourage you to create your own narrative, be relentless, train hard, and most important, enjoy the journey.

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Conflicts of Interest

Dr. Orser is named as an inventor on two patents (Canadian Patent 2,852,978; United States Patent 9,517,265) and one pending patent (United States patent 62/268,137).

Correspondence

Address correspondence to Dr. Orser: Chair, Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada, M5S 1A8. beverley.orser@utoronto.ca. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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