

PREFACE

Although millions of people worldwide are anesthetized every year, we still have no true understanding of why the drugs we use do what they do. This remarkable lack of knowledge limits our ability to design drugs that would minimize or eliminate anesthetic side effects. Indeed, our anesthetic drugs are powerful poisons. The therapeutic index is defined as the lethal dose that kills 50% of the population divided by the effective dose for 50% of the population. For many drugs, the therapeutic index is several hundred or thousand fold; for anesthetics, the therapeutic index is only 3–4. This narrow margin of safety underscores the inherent danger of anesthetics. It is only because of the skill of well-trained anesthesiologists that anesthesia is relatively safe. Nonetheless, whereas serious complications such as death are rare, more bothersome complications (nausea, vomiting) are common, and are terribly distressing for patients. Only by thoroughly understanding how anesthetics exert their effects (good and bad) can we design drugs that will do one thing and one thing only—anesthetize patients, rendering them unconscious, amnestic, and insensible to noxious stimulation.

Neural Mechanisms of Anesthesia represents our current understanding of anesthetic mechanisms. Its emphasis is rather different from other books on the subject, which in the past focused primarily on molecular mechanisms. We have chosen to examine anesthetic mechanisms at multiple levels: the molecule, the cell, organ systems, and the whole body (Fig. 1). This broad overview is necessary, we believe, because it is difficult to grasp the impact and importance of an experimental finding in the absence of the context of the whole animal or human. For example, when a researcher reports that isoflurane enhances opening time of a particular channel, what does that mean to a clinician? How does that action result in the clinically relevant actions of anesthetics (such as unconsciousness)? Furthermore, how much effect on opening time is required to get the relevant result? If the researcher reports that isoflurane at one minimum alveolar concentration enhances channel opening time 10%, is that sufficient to achieve a clinical goal? One can see the fundamental flaw in not being able to link these specific experimental findings with clinical observations. If we knew through some independent means that 50% enhancement (exclusive of any other action, an important and probably incorrect caveat) was required to cause unconsciousness, then we could conclude that this effect on opening time is not relevant. Thus, we must synthesize all the experimental findings at multiple levels in order to determine the relevance of each. Claude Bernard, the eminent 19th century scientist, clearly recognized the folly of narrowly viewing experimental findings:

... If we break up a living organism by isolating its different parts, it is only for the sake of ease in analysis and by no means in order to conceive them separately. Indeed when we wish to ascribe to a physiological quality its value and true significance we must always refer it to this whole and draw our final conclusions only in relation to its effects in the whole—CLAUDE BERNARD, 1865

Each researcher clearly examines the problem of anesthetic mechanisms from a different perspective, not unlike the six blind men of Indostan, who “examined” the elephant, each having different ideas about the elephant’s shape. In the end, though, the blind men had incomplete “visions” of the elephant:

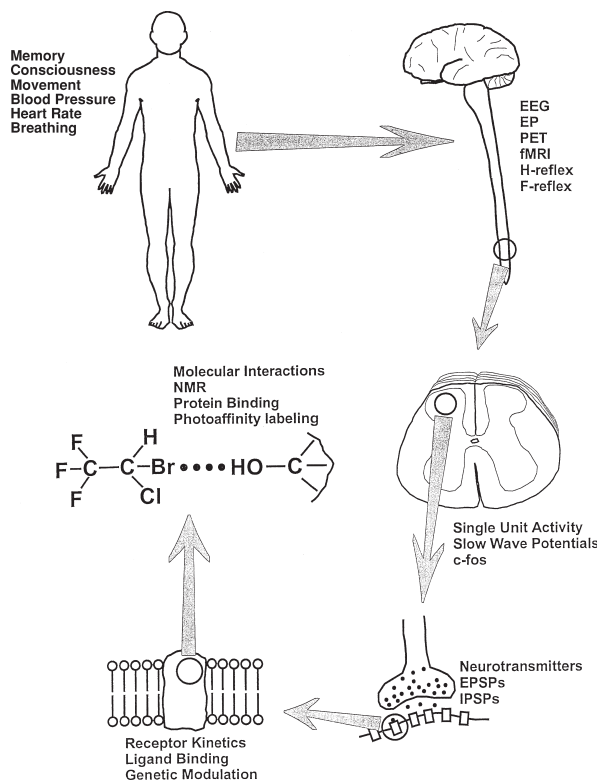


Fig. 1. Anesthesia results in clinically observable effects, such as amnesia, unconsciousness, and immobility. Anesthetic mechanisms must explain these endpoints, and are investigated by study of smaller and smaller components of the organism, such as the brain and spinal cord, the dorsal horn of the spinal cord, the synapse, the cell membrane with its associated receptors and proteins, individual receptors, and finally individual molecules, including molecular interactions between anesthetics and specific sites on proteins and other biological molecules. EEG = electroencephalogram; EP = evoked potentials; PET = positron emission tomography; fMRI = functional magnetic resonance imaging; EPSPs = excitatory postsynaptic potentials; IPSPs = inhibitory postsynaptic potentials; NMR = nuclear magnetic resonance. Other methods to investigate anesthetic mechanisms are available but have been omitted.

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!
—JOHN G. SAXE, *The Blind Men and the Elephant*

So, too, is our understanding of anesthetic mechanisms incomplete. This book will hopefully bridge the gaps that exist between the various views and perspectives of the contributors.

We have separated *Neural Mechanisms of Anesthesia* into six sections. The first section discusses the history of research into mechanisms of anesthesia. The second section covers topics related to consciousness and memory. These chapters are important simply because before we can discuss how anesthetics work, we must decide what they affect. Ablation of nociceptive motor responses, a third critical anesthetic endpoint is included in Chapter 11. The third section includes chapters describing physiological (sleep) and pathophysiological (coma) states related to anesthesia. Section 4 (Neural Mechanisms) reviews the anatomic structures and physiological processes that are likely targets of anesthetics. A well-grounded knowledge of the cerebral cortex, thalamus, reticular formation, and spinal cord will aid the reader's understanding of chapters dealing with anesthetic action at these sites. The fifth section includes cellular and molecular mechanisms. We have included chapters on drugs that are not truly general anesthetics, but are used in clinical practice and can affect the action of general anesthetics (local anesthetics, opiates, neuromuscular blocking drugs). Lastly, we end with a chapter on the future of research into anesthetic mechanisms.

What is anesthesia? This simple question does not have a simple and straightforward answer. Ask any number of individuals and one is likely to get different answers. For the surgeon, general anesthesia consists of an immobile patient. For the patient, general anesthesia consists of amnesia, and not necessarily unconsciousness. That is, patients would likely choose the combination of amnesia and consciousness over the combination of recall and unconsciousness. The latter combination is possible, at least as regards implicit recall. For the anesthesiologist, general anesthesia entails immobility, amnesia, and unconsciousness. Other goals are desirable, but not necessary. Some argue that analgesia is needed, but we disagree. We defend this position first with a semantic argument. Analgesia, in its simplest form, is defined as relief of pain. Pain is the conscious awareness of a noxious stimulus (real or perceived) associated with certain emotional and behavioral patterns, such as withdrawal. Because anesthetized patients are usually unconscious, they do not perceive pain. Of course, they may develop physiological responses to the noxious stimulus (increased heart rate, blood pressure, catecholamine concentrations, etc.). But when awakened and asked if they "felt any pain" they would say: "None—I was completely knocked out." In some patients, amelioration of these physiological responses is desirable (such as those with coronary heart disease). However, in a healthy young patient, a heart rate of 130 bpm and blood pressure of 180/90 mmHg is not injurious. And, whether or not this response is harmful because of a failure to obtain pre-emptive analgesia is open to debate.

Figure 2 summarizes the sensitivities of various anesthetic goals or endpoints. It is important to point out that the sensitivities of memory and consciousness are similar, but that available evidence suggests that memory is more sensitive to anesthetics. These data, however, were developed in human volunteers who were not subjected to noxious stimuli. It is possible that noxious stimulation would shift both the memory and consciousness curves to the right. Because of ethical concerns, these studies have not been performed, and are not likely to be performed. The greater sensitivity of memory parallels the greater sensitivity of memory to other insults, such as trauma and ischemia. For example, minor head trauma can lead to just a few minutes of unconsciousness but hours of amnesia (both retrograde and antegrade). Both memory and unconsciousness are more sensitive than the movement response to noxious stimulation. This is in keeping with the importance of the withdrawal (flight) response. From an evolutionary perspec-

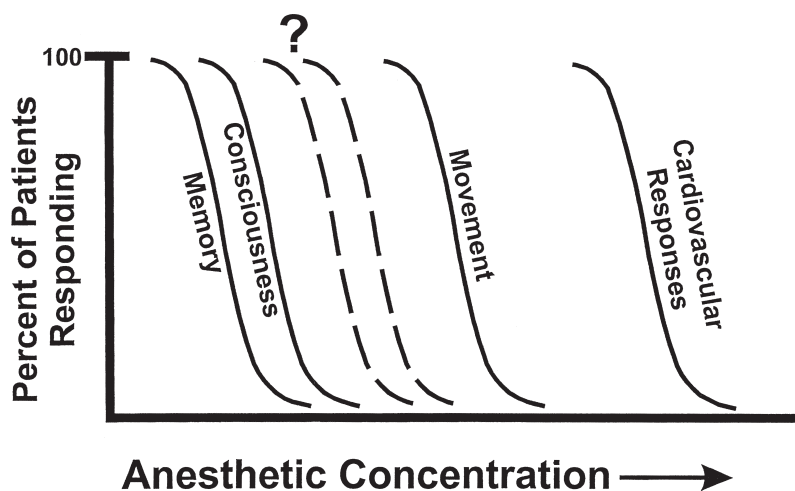


Fig. 2. Anesthetic endpoints have different sensitivities to anesthetics. Memory and consciousness are particularly sensitive, and ablated well below the concentrations needed to prevent movement. The effects on memory and consciousness have been examined primarily in human volunteers in the absence of noxious stimulation. It is quite possible that noxious stimulation shifts the memory and consciousness response curves to the right, although this is not known with certainty (thus, the question mark). Cardiovascular responses to noxious stimulation are very resistant, and require anesthetic concentrations well above those needed to ensure immobility.

tive, the withdrawal response to a noxious stimulus should be hardy and most resistant to physiological insults, as compared to consciousness and memory. Indeed, simple organisms have nociceptive withdrawal responses, but it is unclear whether they experience consciousness in a way similar to humans. These organisms probably do not have memory (as we know it), but they are capable of “learning,” which means that classical conditioning can occur.

Neural Mechanisms of Anesthesia represents the most recent advances in research of anesthetic mechanisms. In part, progress in this research has advanced as a result of our increasing understanding of whole-body, cellular, and molecular processes. The mechanisms of anesthesia are still elusive, but we are closing in. Soon we will be able to design drugs that have specific desired actions, with no undesirable effects. We must continue to carefully judge the risks and benefits of the powerful and dangerous drugs that we use. When describing Morton’s use of ether in Boston, Bigelow wrote: “Its action is not thoroughly understood, and its use should be restricted to responsible persons.” This statement still rings true 150 years later.

The editors wish to thank the contributing authors who have been generous with their expertise, time, and effort. We are also grateful for the expert editorial assistance of Serena Reid at the University of California, Davis. Finally, we thank the staff at Humana Press, including Craig Adams, Paul Dolgert, and Mark Breaugh—we may write the words, but they put the words on paper for the world to read.

Joseph Antognini, MD
Earl Carstens, PhD
Douglas E. Raines, MD



<http://www.springer.com/978-0-89603-997-1>

Neural Mechanisms of Anesthesia

Antognini, J.E. (Ed.)

2003, XII, 466 p., Hardcover

ISBN: 978-0-89603-997-1

A product of Humana Press