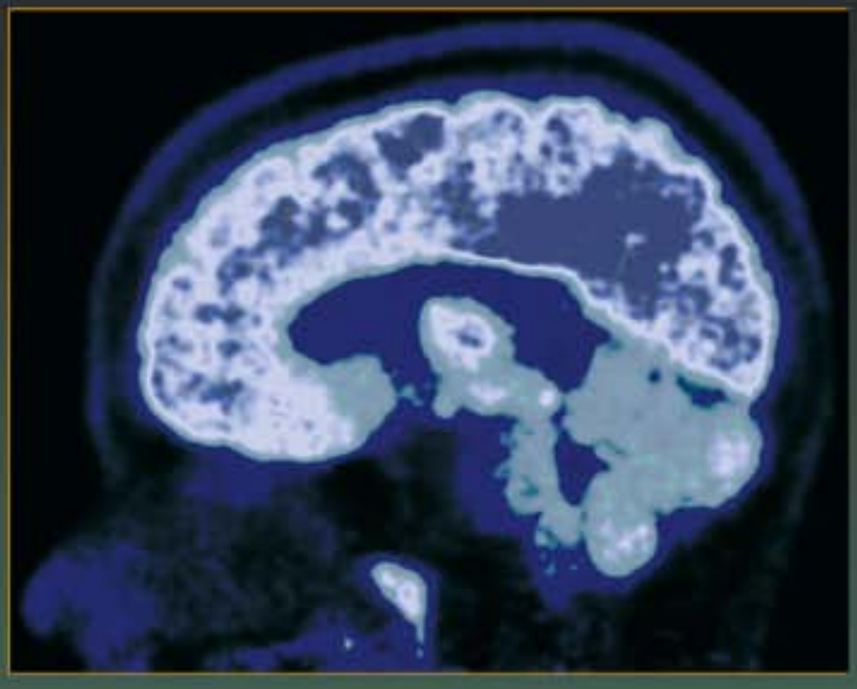
Suppressing the Mind

Anesthetic Modulation of Memory and Consciousness

Edited by
Anthony Hudetz
Robert Pearce



Humana Press

Suppressing the Mind

For further volumes:
http://www.springer.com/series/7678

Anthony Hudetz · Robert Pearce
Editors

Suppressing the Mind

Anesthetic Modulation of Memory and Consciousness

Humana Press

Editors
Anthony Hudetz
Department of Anesthesiology
Medical College of Wisconsin
8701 Watertown Plank Road
Milwaukee WI 53226
USA
ahudetz@mcw.edu

Robert Pearce
Department of Anesthesiology
University of Wisconsin, Madison
B6/319 Clinical Science Center
600 Highland Avenue
Madison WI 53792
USA
rapearce@wisc.edu

ISBN 978-1-60761-463-0 e-ISBN 978-1-60761-462-3
DOI 10.1007/978-1-60761-462-3

Library of Congress Control Number: 2009938710

Printed on acid-free paper

springer.com

Foreword

Anesthetics produce a reversible state of unconsciousness accompanied by anterograde amnesia. This remarkable phenomenon brings great relief to surgical patients and wonder to clinicians and scientists. To date, we do not fully understand the mechanisms by which anesthetics ablate conscious sensation and memory. We are, however, making progress.

This book presents original results as well as overviews of the current state of knowledge of the problem. It is authored by investigators who know the field well; their research at a number of levels has contributed substantially to our current understanding of anesthetic modulation of memory and consciousness. Most of the contributors were presenters at two workshops organized by Dr. Pearce and Dr. Hudetz at the 40th Annual Winter Conference on Brain Research, held at Snowmass Village, Colorado, from January 27 through February 2, 2007. One workshop focused on anesthetic modulation of consciousness and another on anesthetic modulation of memory. Seven of the chapters are based on material presented at these symposia – appropriately updated with new relevant findings. This information is supplemented by chapters on anesthesia and sleep, computational analysis of the state of anesthesia, and the clinical phenomenon of "anesthesia awareness," a topic that has recently received much public attention. With these three additional contributions, the book thus includes 10 chapters.

Several excellent books on consciousness and memory have been published in recent years, but none of these has presented a systematic compilation of studies on anesthetic modulation of memory and consciousness – at least in a unified view of the subject matter. Likewise, several texts have been written about fundamental anesthetic mechanisms, focusing on pharmacological, cellular, and molecular changes. However, no volume has bridged molecular, cellular, integrative, and systems-level effects, as we believe will be necessary to address the core issues of anesthetic mechanisms. This book is intended to fill this need. We hope that by building these bridges between bench and clinical research, new ideas and testable hypotheses will emerge, so that future work will ultimately lead to an integrative theory of anesthetic-induced unconsciousness and amnesia.

There is a long history of interest in unraveling the mechanisms of anesthesia. With the recent introduction of several new investigative methodologies, and as new hypotheses have emerged, there has been a surge in interest from the traditional,

pharmacological, and clinical neurosciences, as well as newer fields, such as cognitive and computational neurosciences. Considering the incredible significance of understanding the neurobiological basis of consciousness and memory, we expect that this interest will continue to grow. This book should appeal to anesthesiologists, neurologists, psychologists, scientists, and anyone interested in anesthesia, consciousness, or memory. We hope that it serves as a reference for the scientific community and provides a useful perspective for future treatments of the subject. As a summary of the current state of knowledge, it should serve as a useful text for graduate students and researchers who wish to engage in anesthesia research. Although a significant part of the information included here is technical, it is written in a style that we hope makes it accessible to a wider audience than simply scientists who are currently engaged in research in the field.

The editors would like to express their sincere thanks to all contributors for their outstanding work. They appreciate the reviewers' suggestions for the inclusion of additional specific topics. Special thanks are due to Patrick J. Marton and Matthew Giampoala at Springer US for the invitation to prepare this book, and for the editorial assistance of Marnie Filstein.

Milwaukee and Madison, WI

Anthony Hudetz, DBM, PhD and
Robert Pearce, MD, PhD

Contents

Contributors

Michael T. Alkire Department of Anesthesiology and Perioperative Care, University of California, Irvine Medical Center, Orange, CA, USA

Helen A. Baghdoyan Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

Matthew I. Banks Department of Anesthesiology, University of Wisconsin, Madison, WI, USA

Hugh C. Hemmings, Jr. Department of Anesthesiology, Weill Cornell Medical College, New York, NY, USA

Anthony Hudetz Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA

Ralph Lydic Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

M. Bruce MacIver Department of Anesthesia, Stanford University School of Medicine, Stanford, CA, USA

George A. Mashour Departments of Anesthesiology and Neurosurgery, University of Michigan Medical School; Ann Arbor, MI, USA

Robert Pearce Department of Anesthesiology, University of Wisconsin, Madison, WI, USA

Misha Perouansky Department of Anesthesiology, University of Wisconsin, Madison, WI, USA

Kane O. Pryor Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Department of Anesthesiology, Weill Cornell Medical College, New York, NY, USA

Jamie Sleigh Department of Anaesthesiology, University of Auckland, Hamilton, New Zealand

Alistair Steyn-Ross University of Waikato, Hamilton, New Zealand

Moira Steyn-Ross University of Waikato, Hamilton, New Zealand

Robert A. Veselis Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, USA; Department of Anesthesiology, Weill Cornell Medical College, New York, NY, USA

Logan Voss Department of Anaesthesiology, University of Auckland, Hamilton, New Zealand

Christopher J. Watson Department of Anesthesiology, University of Michigan, Ann Arbor, MI, USA

Marcus Wilson University of Waikato, Hamilton, New Zealand

Chapter 1
Introduction

Anthony Hudetz and Robert Pearce

Approximately 100,000 patients undergo general anesthesia in the United States every day. It may come as a surprise that, to date, we do not fully understand how general anesthetics work. That is, we do not know how they "put patients to sleep" (as is commonly said) or (as we would say) how they "suppress the mind." We do not really have a much better understanding of how anesthetic agents prevent people or animals from moving, either spontaneously or in response to a painful stimulus, though there is good evidence that the immobilizing effect of anesthetics arises primarily from actions at the level of the spinal cord. Although their ability to prevent movement is evidently of great practical value in permitting surgical procedures to be performed, what patients really desire is that they feel no pain, that they sleep peacefully through their operation, and that they remember nothing afterward. It is quite likely that the hypnotic and amnesic effects of anesthetics, and possibly also their analgesic effects, derive primarily from actions in the brain through their modulation of intricately connected, complex network of hundreds or even thousands of specialized neuron groups. The biochemical and neurophysiological mechanisms of anesthetic action may, therefore, be understandably quite complex. The amnesic (memory erasing) and hypnotic (consciousness erasing) effects of anesthetics remain mysterious for two underlying reasons: we do not understand the neuronal functions that make the brain conscious and allow it to store and recollect events and we also do not know the specific molecular and cellular targets of anesthetics that cause them to interfere with consciousness and memory. Thus, we face two fundamental but interrelated questions: how does the brain work? And how do anesthetics interfere? Understanding the neuronal mechanism of general anesthesia both helps and benefits from research into the neurobiological mechanisms of consciousness and memory.

Why should we be concerned with these questions? Understanding the neurobiological bases of consciousness and memory are arguably two of the greatest challenges for neuroscience. The potential impact of such discoveries for science, medicine, and society is enormous. Knowing what makes people consciously

A. Hudetz (✉)
Department of Anesthesiology, Medical College of Wisconsin, Milwaukee, WI, USA
ahudetz@mcw.edu

A. Hudetz, R. Pearce (eds.), *Suppressing the Mind*, Contemporary Clinical Neuroscience, DOI 10.1007/978-1-60761-462-3_1,

perceive and behave as they do, and how and why they learn, remember, and forget, not only would revolutionize fields of medicine such as neurology, psychiatry, and anesthesiology but would have far-reaching implications for morality, ethics, law, and education.

We believe that anesthesia research can make major contributions in these research endeavors. Anesthetic agents represent an exclusive class of psychoactive drugs that can be used to modulate the states of consciousness and memory in a safe and reversible manner. A century of experience with anesthetic drugs, and the rapidly expanding knowledge of their molecular, cellular, neurophysiological, and psychological actions, make them unique and useful tools to study the neurobiological bases of consciousness and memory. As anesthesiologists remove and restore human consciousness and memory daily, their methods and experience should arguably be a foundation *par excellence* for a scientific understanding of the nature of states of consciousness and memory.

An obvious and direct benefit of this research for anesthesiology is the potential discovery of novel anesthetic drugs. Although general anesthesia is highly reproducible and reversible, all anesthetic agents also have undesirable side effects. Some can be of significant concern, particularly when they are administered to patients with compromised health. Knowing the key mechanisms leading to loss of consciousness or impairment of memory would open the door to the design of new agents with more specific actions, and therefore safer drugs. Understanding the mechanisms of anesthetic-induced unconsciousness and amnesia would have another important benefit: it would aid in the development of novel anesthetic depth monitors based on sound neurophysiologic principles. Many such monitors, which already are used in spite of their limitations, have attracted significant attention, by both medical specialists and the public, because of their potential benefit in minimizing the occurrence of unwanted intraoperative awareness.

This book represents a compendium of data-driven theories. They are based upon the results obtained by research groups who investigate the mechanisms of general anesthesia from a wide range of perspectives. The experimental approaches range from molecular, cellular, and pharmacological to electrophysiological, behavioral, functional brain imaging, and computer simulation, in humans and animals, in vitro and in vivo. An amalgam that includes this diversity of approaches is not a coincidence; it is consistent with our belief that only such a multilevel and interdisciplinary approach will be successful in revealing the mechanisms of anesthesia, particularly for such complex phenomena as consciousness and memory. Clearly, whole fields of research into anesthesia mechanisms cannot be accounted for in 10 chapters. Nevertheless, we feel that the contributions do represent a reasonable sampling of the range of anesthesia research that exists today.

The past two decades have seen dramatic shifts in our thinking about mechanisms of anesthetic action at multiple levels, including the molecular nature of anesthetic targets, how changes in cellular function lead to altered network activity patterns, and which brain regions are associated with specific behavioral effects. Considerable evidence now supports the notion that anesthetic agents act on multiple specific molecular targets, including various ligand-gated, voltage-gated, and

other types of ion channels and proteins, and that their relative abilities to achieve various end points reflect the diversity of these actions. The mechanisms by which volatile agents produce their desired (and undesired) effects are more uncertain than those of intravenous agents; however, significant progress is being made in defining molecular targets as they relate to specific anesthetic end points. Chapter 2 by Hemmings presents an overview of the currently known molecular targets of general anesthetics in the vertebrate nervous system.

A fundamental problem that hinders the bridging of molecular, synaptic, and neurochemical actions of anesthetic drugs to their observable cognitive-behavioral effects on an intact organism is the lack of a rigorous definition of consciousness. What is it exactly that the anesthetics remove? And does the removal of a particular type of brain activity invariably imply the removal of conscious experience? We can observe patient response, movement, and behavior, but not consciousness per se. The definition of memory is also problematic, but at this time memory processes can be more objectively studied. There is a greater difficulty with defining consciousness. Several chapters address the definitional issues for consciousness. To make any progress, a pragmatic approach is necessary. Watson, Baghdoyan, and Lydic define the states of consciousness as "specific traits that include physiological and behavioral measures." Hudetz views consciousness as "subjective experience" but then adopts an objective measure of consciousness in terms of cortical information exchange. Sleigh, in turn, defines the loss of consciousness as a state transition in neuronal population activity.

Clinically, one of the principal assessments of the state of "anesthesia" is the presence or absence of a voluntary response to verbal commands. It is a common supposition that consciousness is lost when the motor response is absent. How secure is this conclusion, and does it apply equally to all anesthetics? The motor response depends not only on sensory perception, but also on the capacity and motivation to respond. Moreover, not all anesthetic agents may affect motor and sensory systems to the same degree, potentially leading to a dissociation of perceptual and volitional consciousness. The most notable "dissociative agents" are the NMDA receptor blockers – ketamine, nitrous oxide, and xenon. However, other agents may share this trait to some extent. Indeed, Banks presents an experimental model in which the effects of isoflurane on motor control and sensory processing are dissociable.

The chapter by Watson et al. presents a comprehensive review of complex subcortical systems that control wakefulness and sleep, including "rapid eye movement" (REM) and non-REM sleep. It emphasizes implications for the mechanism of anesthesia. The authors hypothesize that anesthetics work by altering endogenous neurochemical systems that regulate sleep and wakefulness. There is already clear evidence for this hypothesis, at least for certain receptor-specific agents such as alpha 2 adrenergic agonists. Neuron groups of critical importance are found in various subcortical nuclei, including the thalamus, select regions of the hypothalamus, pontine reticular formation, raphe nuclei, locus ceruleus, nucleus basalis, and other basal forebrain nuclei. Most of these nuclei can exert wake-promoting or sleep-promoting effects, with specific effects on REM and non-REM sleep, depending on

the neurotransmitters and receptor subtypes used. It is clear that this is a very complex network and that a great deal more research will be necessary to help assemble the details of current knowledge into a quantitative model of network interactions that regulate sleep–wake transitions. Proper functioning of this system is critical to enable consciousness and memory encoding that takes place in the cortex and the hippocampus. In turn, anesthetics can interfere with consciousness and memory by disrupting this subcortical "enabling system" at multiple points. Which points actually do serve causal roles as anesthetic targets, and how the entire system is impacted by pharmacological activation of specific nuclei, such as the central medial thalamus, through which consciousness, or at least wakeful behavior, can be restored (as described in the chapter by Alkire), are promising avenues for future research.

Several common themes emerge in the contributions by various authors. One of these is the phenomenon of neuronal synchronization. The importance of neuronal synchronization for information processing is now widely recognized. The brain's ability to synchronize the activity of functionally related neuronal populations, evident in local field potentials as well as in single-unit activity, is thought to be critical to the formation of "percepts." Activation of synchronous neuronal inputs also supports neuronal plasticity, and thus learning and memory. It would make sense, then, if synchrony were suppressed under anesthesia, as this might lead to loss of consciousness and impaired memory. A hallmark of both sleep and anesthesia is, however, the appearance of dominant slow, periodic waves in the spontaneous EEG, commonly referred to as "synchronization." Perouansky reports that not only is the hippocampal theta rhythm preserved under amnesic concentrations of inhaled agents, but it is even enhanced by some anesthetics, such as halothane. Banks reports that isoflurane, an anesthetic agent that prolongs postsynaptic inhibitory current, actually increases spike synchrony in cortical neurons. Perhaps the activity of the brain under anesthesia would more appropriately be termed "hypersynchronization"?

Another general finding, one that is addressed by several contributors (and is related to the issue of synchronization), is that under anesthesia at a hypnotic level, the brain preserves its primary reactivity to sensory stimuli. Banks finds that the magnitude of cortical auditory-evoked responses is augmented, and Hudetz finds the same with visual stimulation. MacIver cites similar evidence from other laboratories. In all, this implies that hypnosis (loss of consciousness) should not be equated with thalamic (or other) deafferentation of the cortex. Although anesthetic effects on subcortical relays may alter sensory information en route to the cortex, the emerging view is that changes in the evoked oscillation frequency and unit synchrony may garble the orderly information flow to the point it cannot gain access to consciousness.

Several chapters endorse a "corticocentric" view of anesthetic action. This represents a departure from the more traditional view that emphasizes the role of the ascending activating system, including relevant nuclei of the thalamus, in controlling consciousness. The cerebral cortex as a primary target of volatile anesthetic agents in particular, with loss of connectivity of neuronal populations as a potential mechanism of anesthesia, receives support from multiple quarters. It

is supported by studies in functional brain imaging (Alkire), auditory perception (Banks), EEG coherence (Hudetz), and computer simulation (Sleigh). Nevertheless, given the clear role of the thalamus in controlling states of consciousness, and the emerging view that cortical integrative functions may to a large degree depend on thalamo-corticothalamic connections, a possible role for anesthetic modulation of thalamic elements must still be considered. Alkire discusses in detail the possible involvement of the thalamus in anesthesia with respect to unconsciousness. A consistent suppression in thalamic activity is observed with many anesthetic agents, but whether this is due to a direct effect on the thalamus or secondary to a suppression of corticothalamic feedback remains an important unanswered question.

From a number of contributions, a general hypothesis for anesthetic-induced unconsciousness emerges at an integrative level. Several contributors emphasize the role anesthetics may play in disrupting cortical information integration necessary for conscious perception, and possibly consciousness itself. As Alkire and Hudetz point out, there may be certain cortical regions with a particularly critical role in consciousness, for example, association regions of the posterior parietal cortex that are involved in multisensory integration, attention, and resting state activity. Brain imaging studies suggest that the activity of this region may be a primary target of anesthetics. Another emerging integrative model of unconsciousness invokes the role of top-down processes, as argued by both Banks and Hudetz. Top-down or feedback modulation of sensory cortical activity at rest and during sensory input has been postulated to play a critical role in attention and contextual interpretation of sensory information. Both authors report that bidirectional recurrent activity between primary sensory and higher association regions is disrupted by general anesthesia, as observed in EEG coherence, local field potentials, and unit synchronization, in a manner that correlates with anesthetic-induced loss of consciousness.

Computer simulations represent a novel and interesting approach to better understand the effect of anesthetics on neuronal network operations. The complexity and interconnectedness of cortical brain circuits calls for a quantitative modeling to understand the dynamics of activity of this system under normal conditions and under the influence of drugs with known synaptic effects. Sleigh presents a continuum model of the activity of a population of cortical excitatory and inhibitory neurons that predicts a state transition in the form of an abrupt change in the simulated EEG. This is explained by a loss of neuronal connectivity, which is proposed to serve as an indication of the loss of consciousness. Two contributors (Sleigh and Hudetz) elaborate on the significance of network topology as a potential determinant of how and why general anesthetics may disrupt functional systems of the brain. As already recognized, higher cognitive operations, and likely consciousness itself, depend on a high degree of integration that involves large-scale networks of the brain. Network organization appears to follow the "small world" model, characterized by hubs with high local connectivity and tied together by sparse long-range interconnections. This topology is efficient and economical, and it influences how diffuse lesions or drug-induced modulation of neurotransmission may affect connectivity of the system as a whole. It may also highlight vulnerabilities of the