REVIEW ARTICLE

MECHANISM OF UNCONSCIOUSNESS: WHAT WE KNOW FROM BASIC SCIENCE

Dr. Priyam Saikia M.D.
Professor (DACP)
Anaesthesiology and Critical Care
Gauhati Medical College and Hospital
Email: saikia.priyam80@gmail.com

Abstract: *This review explores the mechanisms of unconsciousness from an anaesthesiology perspective, defining consciousness through clinical characteristics such as wakefulness and awareness. General anaesthesia induces a unique, reversible state distinct from natural sleep, where unresponsiveness does not necessarily equate to unconsciousness. This review article examines the Neural Correlates of Consciousness (NCC) and neurophysiological mechanisms, detailing how anaesthetics disrupt information integration across cortical and subcortical networks. Furthermore, it discusses neurochemical mechanisms, specifically the modulation of neurotransmitters like GABA and NMDA, and ion channels, which underpin the loss of consciousness.*

Keywords: *General Anaesthesia, Unconsciousness, Neural Correlates of Consciousness (NCC), Neurotransmitters, GABA Receptors, Cortical Connectivity, Neurophysiology.*

In this review, constrained by the permitted word limit, I will try to explore the essence of consciousness, defining a few of its characteristics, and then seek to understand unconsciousness from an anaesthesiology viewpoint followed by a brief examination of the mechanisms underlying its different attributes.

I. Consciousness and its perspective from Anaesthesiology

The exploration of consciousness spans multiple disciplines, including clinical medicine, philosophy, physics, psychology, neurobiology, mathematics, and computer science. These diverse engagements have advanced various viewpoints, complicating efforts to integrate and compare insights. Thus, there are various definitions of `consciousness` and a central challenge is the absence of a consistent definition.[1] Within my judgment capabilities, perhaps the perspective that consciousness is "the ability to maintain an alert state, attention, and awareness of self and environment" embodies most of the contributes from the perspective of medical science. [2]

The philosophical perspective distinguishes two aspects of consciousness. The phenomenal consciousness is the subjective "what it feels like" aspect, and access consciousness, the cognitive availability for reasoning and behaviour. [3]

From the perspective of a clinician, consciousness can be examined through its primary clinical characteristics—wakefulness, awareness, and responsiveness. [3] It is the practical framework that is used by us anaesthesiologists. Wakefulness, or the level of arousal, is the capacity to open one's eyes, either spontaneously or in response to a stimulus. [3] Awareness is divided into two aspects: internal awareness, which includes mental activities such as inner speech and mind wandering, and external awareness, which involves consciously perceiving the environment through sensory channels. These facets shape our overall conscious experience, balancing internal thoughts with external stimuli. [3] Conscious behaviour depends on sufficient arousal (i.e., being awake) and awareness of content (i.e., sensory, cognitive, and emotional experiences). [4] Global Neuronal Workspace Theory (GNWT), Higher-Order Theories (HOT), Integrated Information Theory (IIT), Recurrent Processing Theory (RPT), and Predictive Processing (PP) are prominent theories that seek to explain the nature of consciousness in the realms of neuroscience. [5] Discussions on consciousness, sleep, and anaesthesia are frequently complicated by a multitude of confusing, often tautological, and partially overlapping terms, such as "consciousness," "awareness," "responsiveness," "wakefulness," "arousal," "hypnosis," "sleep," and "sedation" etc. [6] As a clinical correlate

of consciousness, awareness is frequently assessed in clinical anaesthesiology practice. [6] From a clinical standpoint consciousness is often divided into two components: arousal (wakefulness) and awareness (of self and environment). [7] In this context, "awareness" refers to both consciousness and the clear recall of events during surgery. [7]

II. Unconsciousness and its perspective from Anaesthesiology

Similar to consciousness, unconsciousness has been approached from various perspectives depending on the scientific field, each emphasizing different aspects such as neural mechanisms, clinical assessment, or cognitive processes. Unconsciousness is a pillar of anaesthesia. [4] General anaesthesia is a medically induced, reversible state characterized by unconsciousness, memory loss, pain relief, and muscle relaxation, while maintaining stable autonomic, cardiovascular, respiratory, and thermoregulatory functions. [8] The reversible nature of general anaesthesia induced unconsciousness distinguishes it as a unique state.

In the context of anaesthesiology, unconsciousness induced by general anaesthesia is not a singular state but encompasses distinct states that vary based on the presence or absence of subjective experience, environmental perception, and responsiveness. [3, 6] Unconsciousness in anaesthesia may manifest as complete unconsciousness (no subjective experience), disconnected consciousness (dream-like states without environmental perception), or connected consciousness (episodic awareness of self and environment). [3, 6] Connected consciousness may not be associated with its explicit recall. [3] Unresponsiveness is frequently equated with unconsciousness but unresponsiveness does not equate to unconsciousness. [6] Patients may be unresponsive due to muscle relaxants (e.g., succinylcholine) or subcortical suppression but still experience connected or disconnected consciousness. [6]

III. Mechanisms of unconsciousness during anaesthesia

The notion that consciousness arises from brain activity places neural correlates of consciousness (NCC) at the forefront of understanding the

mechanisms of both consciousness and unconsciousness. [3] NCC refers to a minimal set of neuronal mechanisms sufficient for any phenomenological aspect of consciousness to emerge. [3] Neurotransmitter systems play a critical role in modulating the brain's functional mechanisms that underpin conscious experience. [3] It is not surprising that distinct NCC and neurotransmitter systems are implicated in various attributes across the spectrum of anaesthesia-induced unconsciousness.

Thus, the mechanisms underlying unconsciousness during anaesthesia are primarily explained through neurophysiological and neurochemical frameworks. The mechanisms of general anaesthesia have been studied using various animal models and cell lines. [9] Studies using in vitro sensitivity, in vivo sensitivity, direct binding (via photolabeling and structural studies), and in vivo regulation (genomic/proteomic techniques) have been used to elucidate the mechanism of action of these agents at molecular, cellular, and neuronal network levels. [9]

III.a Neurophysiological mechanisms

The neural correlates of anaesthesia have been studied using EEG, fMRI, and PET. [3,8] Cutting-edge neuroscience techniques, such as optogenetics, chemogenetics, and targeted genetic methods, have advanced understanding of these circuits.[9] General anaesthetics induce unconsciousness by acting on multiple neural circuits in both cortical subcortical brain regions. Studies reveal that anaesthesia alters brain communication, particularly in the prefrontal, parietal, and posterior regions to modulate consciousness states. [3] General anaesthetic agents generate agent-specific, unique and dose-dependent EEG, fMRI, and PET patterns. [3, 10, 11] Thus some anaesthetics tap into sleep-related neural pathways to cause unconsciousness. [3, 10, 11] Additionally, anaesthetics suppress wakefulness by directly inhibiting cortical neurons and subcortical arousal-promoting neurons. [3, 10, 11] Propofol alters cortical activity, particularly in the default mode network and frontoparietal networks, which are associated with self-awareness and attention. [12] Subcortical regions, including the brainstem, hypothalamus, and basal forebrain, play a role in regulating arousal and are targeted by anaesthetics. [13] Anaesthetics suppress subcortical arousal systems, contributing to the loss of

consciousness by reducing cortical activation. [13] Brown et al.` s review is an excellent source for those interested in neural corelates of general anaesthesia agents and the molecular pathway involved. [13] Apart from the dispersion of specific NCC, anaesthetics disrupt the brain's ability to integrate information across distributed networks, a process thought to be essential for consciousness. [3, 8, 14] General anaesthetics fragment neural networks, reducing the brain's capacity for integrated information processing. [3, 8, 14] This is reflected in decreased measures of brain complexity, such as entropy, reduce neural complexity and connectivity in large-scale brain networks correlated with unconsciousness. This loss of information integration sets it apart from natural sleep. [8, 14] There is evidence both supporting and challenging the theories of neural correlates (GNWT, IIT and RPT) of consciousness and anaesthesia. [3] Mashour and Hudetz propose that general anaesthetics modulate consciousness through two distinct mechanisms: bottom-up pathways, which suppress subcortical arousal systems and reduce the level of consciousness, and top-down mechanisms, which disrupt cortical connectivity and degrade the content of consciousness. [15] Different anaesthetics affect these dimensions to varying degrees. [15]

III.b Neurochemical mechanisms-

Brain cells communicate through a diverse array of chemical neurotransmitters, which are released into the synapse in response to electrical signals within the neural circuits. Neurotransmitters are broadly categorized as excitatory (glutamate and acetylcholine) or inhibitory [γ-aminobutyric acid (GABA) and glycine]. [16, 17] Excitatory neurotransmitters promote depolarization of the postsynaptic membrane, while inhibitory neurotransmitters suppress it. These neurotransmitters interact with ion channel receptors, regulating ion flow and, consequently, cellular electrical activity. Different types of receptors are associated with different aspects of reduced consciousness such as sedation, amnesia, nociception etc. [7, 16, 17]

The GABA type A ($GABA_A$) receptor is a primary target for many general anaesthetics, particularly inhalational agents (e.g., isoflurane, sevoflurane) and intravenous agents (e.g., propofol, etomidate). [16, 17] These drugs enhance GABA mediated inhibitory neurotransmission by binding to specific

sites on the $GABA_A$ receptor, increasing chloride ion conductance and hyperpolarizing neurons. This results in reduced neuronal excitability, contributing to sedation and unconsciousness. Propofol bind to a site in the transmembrane domain of the $GABA_A$ receptor, allosterically enhancing GABA binding affinity or prolonging channel open time. [16] Several anaesthetics have been found to decrease the desensitization of $GABA_A$ receptors. [16] At higher concentrations, they can directly activate the receptors even in the absence of GABA. [16] N-methyl-D-aspartate (NMDA) receptors, which mediate excitatory neurotransmission, are inhibited by certain anaesthetics, notably ketamine and nitrous oxide. By blocking glutamate binding or channel activity, these agents reduce excitatory signalling, contributing to dissociative anaesthesia and analgesia. [16, 17] Two-pore domain potassium (K2P) channels, such as TREK-1 and TASK-3, are activated by volatile anaesthetics, leading to neuronal hyperpolarization. This enhances potassium efflux, stabilizing the resting membrane potential and reducing excitability. [16,17] General anaesthetics also interact with additional ion channels and receptors, including glycine receptors, voltage-gated sodium channels, and HCN (hyperpolarization-activated cyclic nucleotide-gated) channels. [16,17] These interactions contribute to the multifaceted effects of anaesthetics, such as muscle relaxation and amnesia.

Conclusion

There is substantial evidence that general anaesthesia comprises multiple distinct pharmacological effects, likely involving different neural circuits and acting through separate molecular targets. Recent advances have elucidated anaesthetic binding sites at atomic resolution. [9] However, challenges remain, including understanding the synergy between multiple targets, the differential effects of anaesthetics across brain regions and different aspects of unconsciousness. It is worth noting that emergence from anaesthesia involves distinct arousal pathways (e.g., cholinergic, dopaminergic, histaminergic, and orexinergic), with evidence suggesting that activating these pathways (e.g., via nicotine or dopamine stimulation) can hasten recovery. [18] Despite their widespread use, the precise neural correlates and molecular mechanisms underlying their effects remain

incompletely understood. Understanding the detailed mechanism of action will hopefully provide strategies to separate desirable effects (e.g., amnesia) from adverse outcomes (e.g., postoperative delirium). Understanding anaesthetic mechanisms could advance broader neuroscience questions, such as the nature of consciousness and memory formation.

References

1. Sattin D, Magnani FG, Bartesaghi L, Caputo M, Fittipaldo AV, Cacciatore M, Picozzi M, Leonardi M. Theoretical Models of Consciousness: A Scoping Review. Brain Sci. 2021 Apr 24;11(5):535. doi: 10.3390/brainsci11050535.
2. Yu L, Blumenfeld H. Theories of impaired consciousness in epilepsy. Ann N Y Acad Sci. 2009;1157:48-60.
3. Montupil J, Cardone P, Staquet C, Bonhomme A, Defresne A, Martial C et al. The nature of consciousness in anaesthesia. BJA Open. 2023 Sep 26;8:100224. doi: 10.1016/j.bjao.2023.100224.
4. Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S et al. Comprehensive systematic review update summary: Disorders of consciousness: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology. 2018;91:461-470.
5. Mudrik L, Boly M, Dehaene S, Fleming SM, Lamme V, Seth A et al. Unpacking the complexities of consciousness: Theories and reflections. Neurosci Biobehav Rev. 2025 Mar;170:106053. doi: 10.1016/j.neubiorev.2025.106053.
6. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. Anesthesiology. 2012;116:946-59.
7. Mashour GA, Orser BA, Avidan MS. Intraoperative awareness: from neurobiology to clinical practice. Anesthesiology. 2011;114:1218-33.
8. Brown EN, Lydic R, Schiff ND. General anesthesia, sleep, and coma. N Engl J Med. 2010;363:2638-50.
9. Hemmings HC Jr, Riegelhaupt PM, Kelz MB, Solt K, Eckenhoff RG, Orser BA et al. Towards a Comprehensive Understanding of Anesthetic Mechanisms of Action: A Decade of Discovery. Trends Pharmacol Sci. 2019;40:464-481.
10. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science. 2008;322:876-80.
11. Moody OA, Zhang ER, Vincent KF, Kato R, Melonakos ED, Nehs CJ et al. The Neural Circuits Underlying General Anesthesia and Sleep. Anesth Analg. 2021;132:1254-1264.
12. Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010;113:1038-53.

13. Brown EN, Purdon PL, Van Dort CJ. General anesthesia and altered states of arousal: a systems neuroscience analysis. Annu Rev Neurosci.2011;34:601-28.
14. Mashour GA, Hudetz AG. Neural Correlates of Unconsciousness in Large-Scale Brain Networks. Trends Neurosci. 2018;41:150-160.
15. Mashour GA, Hudetz AG. Bottom-Up and Top-Down Mechanisms of General Anesthetics Modulate Different Dimensions of Consciousness. Front Neural Circuits. 2017 Jun 20;11:44. doi: 10.3389/fncir.2017.00044.
16. Son Y. Molecular mechanisms of general anesthesia. Korean J Anesthesiol. 2010;59:3-8.
17. Forman SA, Chin VA. General anesthetics and molecular mechanisms of unconsciousness. Int Anesthesiol Clin. 2008;46:43-53.
18. Zhang D, Wei Y. Distinct Neural Mechanisms Between Anesthesia Induction and Emergence: A Narrative Review. Anesth Analg. 2025;141:162-171.

Acknowledgements- I would like to acknowledge Dr Abhijit PM (PGT, Anaesthesiology, GMCH) for his input on the first draft. I acknowledge the use of Grok, an AI language model developed by xAI, for assistance with English language editing. After using these tools, I reviewed and edited the content and take full responsibility for the content of the published article.