

Mini Review

Consciousness and Anaesthesia: Anatomical Basis of The Action of Anaesthetics

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Abstract

Consciousness emerges from dynamic interactions among the brainstem, thalamus, basal forebrain, and cerebral cortex. General anaesthesia reliably produces profound unresponsiveness and is generally associated with loss of conscious awareness, yet the underlying mechanisms remain incompletely understood. Here we review the anatomical and neurophysiological substrates of consciousness and examine how anaesthetics modulate these systems. Classical studies established the role of the ascending reticular activating system (ARAS) and thalamocortical circuits in wakefulness. Contemporary research has identified key GABAergic nuclei in the rostromedial tegmentum (RMTg), mesopontine tegmental anaesthesia area (MPTA), and thalamic reticular nucleus (TRN) that contribute to sedation and changes in arousal. General anaesthetics primarily enhance inhibitory neurotransmission via GABA receptors, disrupt cortico-cortical connectivity, and alter thalamic relay function. NMDA-receptor antagonists such as ketamine induce a distinct dissociative state by altering glutamatergic transmission. Recent and speculative research has also proposed that anaesthetics may interact with neuronal microtubules, an idea discussed in relation to the Orch-OR hypothesis. Understanding these anatomical mechanisms provides a framework for managing disorders of consciousness and developing targeted therapeutic strategies.

Introduction

Consciousness is not localised to a single centre; rather, it is an emergent property of distributed neural networks involving the brainstem, thalamus, basal forebrain, and cerebral cortex. These systems collectively support arousal, awareness, and the integration of sensory and cognitive information. The anatomical basis of consciousness became clearer with foundational neuropathological observations by von Economo during 1917 to 1930 [1], who described lesions in the upper brainstem tegmentum in patients with encephalitis lethargica, establishing the importance of this region for wakefulness. Later, the landmark physiological experiments of Moruzzi and Magoun in 1949 [2] identified the ascending reticular activating system (ARAS), a diffuse network projecting to the thalamus and cortex, forming an important substrate for arousal. Penfield in 1938 further demonstrated the integrative role of the “centrencephalic system” linking the brainstem, thalamus, and cortex [3]. The historical development of Penfield’s concept and its relationship to the physiology of mind has subsequently been discussed

[4]. Modern neuroimaging, electrophysiology, and molecular neuroscience have significantly advanced our understanding of consciousness. High-resolution MRI, magnetoencephalography (MEG), and intracranial recordings highlight the critical role of thalamocortical loops, with the thalamic reticular nucleus (TRN) modulating cortical rhythms essential for conscious experience. At the cortical level, posterior cortical regions, including the temporo-parietal and occipital association cortices, appear crucial for the contents of consciousness, while frontal regions contribute to executive integration. General anaesthetics, including volatile agents, propofol, benzodiazepines, ketamine, and others, act by targeting specific nodes in these systems. Many commonly used anaesthetic agents potentiate inhibitory GABAergic transmission, while others, particularly ketamine, act through NMDA receptor antagonism and associated network effects. At a network level, anaesthetics can fragment cortical connectivity, reduce global integration, and impair recurrent processing, all of which are associated with anaesthetic-induced alterations in consciousness. Despite the longstanding clinical use of anaesthesia since Morton's demonstration of ether in 1846, the precise mechanisms remain incompletely defined. This review synthesizes classical and contemporary evidence on the anatomical and neurophysiological basis of anaesthetic-induced changes in consciousness, including emerging and speculative microtubule-level theories, and discusses implications for disorders of consciousness.

Discussion

Anatomical Substrates of Consciousness

Brainstem: The foundation of arousal

The brainstem reticular formation is one of the oldest identified systems essential for wakefulness. The ARAS, originating in the pontine and midbrain tegmentum, projects to the thalamus, basal forebrain, and cortex. Interruption of critical components of this pathway can produce profound impairment of consciousness and arousal [2-4]. GABAergic nuclei in the brainstem, particularly the rostromedial tegmental nucleus (RMTg) and mesopontine tegmental anaesthesia area (MPTA), regulate sedation and anaesthetic sensitivity [5, 6]. Activation of RMTg neurons can enhance anaesthetic effects, while manipulation of these pathways can alter sensitivity to anaesthetic agents.

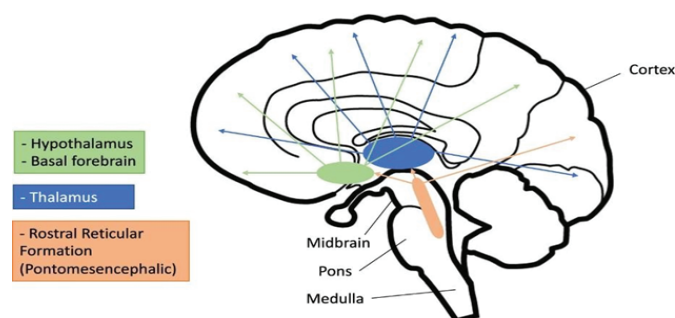


Figure 1: Outline of the human brain showing the areas involved in arousal and wakefulness. The figure illustrates brainstem nuclei, ARAS pathways, and projections to the thalamus and cortex that are essential for wakefulness.

Thalamus: The central relay

The thalamus integrates ascending sensory input and distributes it to cortical association networks. Central lateral thalamic neurons show state-dependent firing patterns that correlate with changes in consciousness. The thalamic reticular nucleus (TRN), receiving fibres from thalamic and cortical systems, modulates thalamocortical rhythms essential for awareness. MEG studies by Llinás and Ribary demonstrated coherent thalamocortical oscillations associated with human conscious states [7]. Anaesthetics can depress thalamic relay function and alter communication between the thalamus and cerebral cortex, thereby reducing the effective transmission and integration of information. Cortical consciousness depends on long-range connectivity among association cortices. Layer 5 pyramidal neurons provide important connections between cortical regions and the thalamus, and experimental studies have demonstrated that general anaesthesia can decouple cortical pyramidal neurons and disrupt feedback signalling [8]. Loss of posterior cortical connectivity has also been observed during propofol-induced loss of consciousness. Changes in connectivity between posterior cortical regions and other areas of the brain have been associated with anaesthetic-induced alterations in consciousness [9].

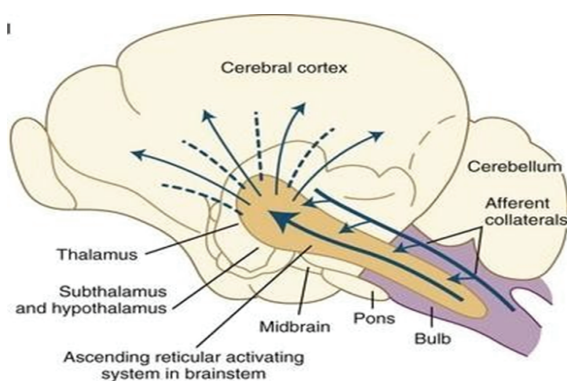


Figure 2: Brainstem reticular formation and ascending projections. The figure shows classical ARAS pathways identified by Moruzzi and Magoun and their functional relevance to consciousness.

Mechanisms of Anaesthetic Action

GABAergic enhancement

Most general anaesthetics, including propofol and several volatile anaesthetics, potentiate GABAergic inhibition. Activation or potentiation of GABA_A receptors increases inhibitory chloride currents and reduces neuronal excitability. Benzodiazepines also enhance GABA_A-mediated inhibition, although their clinical effects and mechanisms differ from those of general anaesthetic agents such as propofol. At the systems level, GABAergic anaesthetics alter neuronal activity in brainstem and cortical networks and can disrupt communication between thalamic and cortical regions. These changes contribute to sedation, immobility, amnesia, and loss of responsiveness [10].

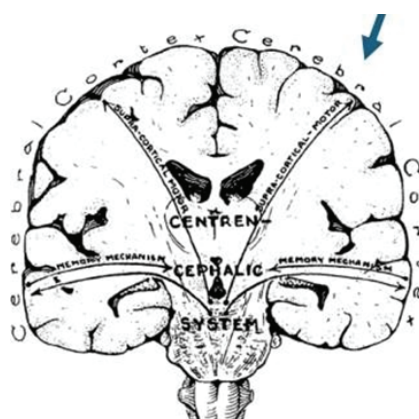


Figure 3: Coronal section of the brain depicting the centrencephalic system described by Penfield. The figure demonstrates integrative pathways connecting the upper brainstem, thalamus, and bilateral cerebral hemispheres.

NMDA antagonism

Ketamine acts primarily as an NMDA receptor antagonist and produces a distinctive dissociative state. Its effects involve changes in glutamatergic transmission and cortical network activity, resulting in dissociation, analgesia, altered perception, and other distinctive subjective effects [11]. Nitrous oxide also has multiple molecular and network actions, including effects involving NMDA receptors, but its anaesthetic mechanism should not be reduced to NMDA receptor blockade alone. Anaesthetics can reduce coherence between the thalamus and cortex, lowering information integration and recurrence. Alkire et al. demonstrated the importance of functional disconnection and impaired cortical communication in anaesthetic-induced changes in consciousness [12].

Microtubules as targets

Hameroff and Penrose proposed the Orch-OR hypothesis, in which quantum processes associated with neuronal microtubules are proposed to contribute to consciousness [13]. Experimental and theoretical work has subsequently explored whether anaesthetic molecules may interact with microtubular structures. Craddock et al. proposed that anaesthetics may act through quantum channels associated with brain microtubules and may influence microtubular processes [14]. However, this remains a speculative hypothesis, and current evidence does not establish microtubules as an established mechanism of general anaesthetic-induced unconsciousness. Therefore, microtubule-level mechanisms should be considered an emerging and speculative area of investigation rather than an established explanation of anaesthetic action.

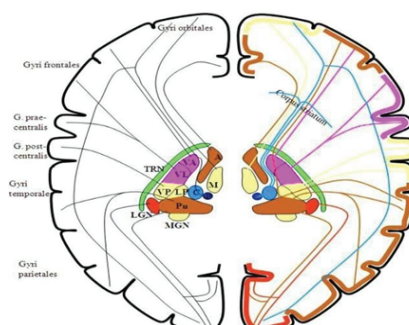


Figure 4: Thalamocortical circuits involved in consciousness. The figure depicts reciprocal connectivity between thalamic relay nuclei, the thalamic reticular nucleus, and cortical layers, including layer 5 pyramidal neurons.

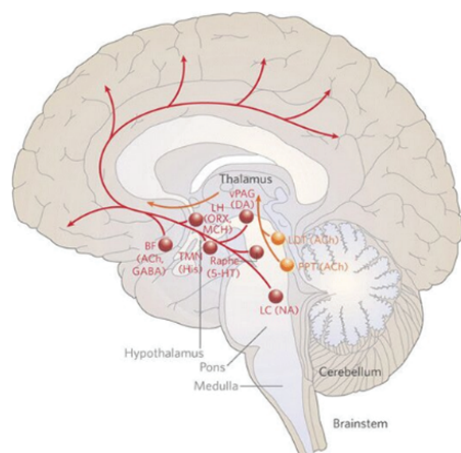


Figure 5: Neurotransmitter systems associated with anaesthetic action. The figure highlights GABAergic, glutamatergic, and other neurotransmitter pathways relevant to sedation and altered consciousness.

Integrated Mechanisms and Future Directions

General anaesthesia produces profound changes in consciousness and responsiveness by acting at multiple hierarchical levels of the neural systems associated with arousal and conscious processing. Classical GABAergic mechanisms within the brainstem and thalamic systems remain important, but modern evidence emphasizes the importance of network-level disruption, particularly thalamocortical dysconnectivity and reduced cortical integration. Distinct classes of anaesthetics demonstrate that anaesthetic-induced changes in consciousness are not a single uniform phenomenon. GABAergic agents can induce profound suppression of responsiveness, ketamine produces a distinctive dissociative state, while dexmedetomidine produces a state with some features resembling non-REM sleep. These diverse pathways illustrate that conscious states depend on intact ascending arousal, thalamic relay, and widespread cortico-cortical communication. The integration of classical neuroanatomy with modern functional imaging and electrophysiology provides a more complete model of the anaesthetic state. Future directions include:

- targeted manipulation of thalamic nuclei to influence recovery from anaesthesia;
- network-based markers to assess depth of anaesthesia;
- further investigation of thalamocortical and cortico-cortical connectivity; and
- emerging molecular theories, including possible microtubule-level interactions.

Understanding these mechanisms also informs the clinical assessment of coma, vegetative state, and minimally conscious state, in which similar disruptions of arousal and large-scale neural connectivity may occur. From an Indian philosophical perspective, deep meditative states may involve altered GABAergic or thalamocortical modulation, although empirical evidence remains insufficient and requires further scientific investigation.

Conclusion

Consciousness arises from integrated activity across brainstem arousal systems, thalamocortical loops, and cortical association networks. General anaesthetics disrupt these circuits through multiple mechanisms, including GABAergic potentiation, NMDA receptor antagonism in agents such as ketamine, and impaired thalamocortical and cortico-cortical communication. Emerging molecular theories propose microtubule-level interactions as an additional possible pathway, although their contribution to consciousness and anaesthetic-induced unconsciousness remains uncertain. Understanding the anatomical and physiological basis of anaesthetic action enhances clinical management of anaesthesia and provides insights into disorders of consciousness and future therapeutic strategies.

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