# Anaesthesia and sleep: Where are we now?

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## Abstract

The mechanisms regulating the control of consciousness in both spontaneous sleep-wake behaviour and general anaesthesia remain poorly understood and are a fundamental question in neuroscience. The last 30 years have identified numerous molecular substrates and more recently important monoaminergic neuronal substrates. Future work now needs to concentrate on elucidating the convergence of these neuronal circuits to build a unifying mechanism of consciousness control.

## **Keywords**

Sleep, general anaesthesia, thalamus, hypothalamus, translational medicine, animal models, human, neocortex

# Introduction

Sleep is a commonly used analogy for general anaesthesia of patients and the reasons are easy to appreciate; sleep is a naturally occurring physiological process characterised by unconsciousness during which conscious perception of the external environment is lost whilst self-body perception is somewhat comparable during oneiric experience. Indeed, general anaesthesia and natural sleep share many physiological hallmarks including an electroencephalogram (EEG) pattern of activity dominated by slow synchronous cortical waves, body immobility and reduction in core body temperature,<sup>1</sup> but Do they really involve the same neurological processes? This concept has enjoyed something of a resurgence in recent years whereby several hypothalamic sleepmediating nuclei have been identified as potential putative neuronal substrates for general anaesthesia.<sup>2-6</sup> Here, we will summarise these data, focusing on the hypothalamus and forebrain structures and discuss where future research should focus to understand better the common and divergent substrates in the brain supporting both sleep, general anaesthesia and consciousness.

# Sleep and anaesthesia: Unknown mechanisms and common brain rhythms/shared circuits?

General anaesthetics are a chemically diverse group of molecules sharing a common endpoint: unconsciousness – one of the critical endpoints for clinical anaesthesia. Their anatomical targets and the connected underlying neural substrates are poorly understood and may differ greatly between agents.<sup>1,7–9</sup> Volatile anaesthetics (e.g. halothane and isoflurane) produce a strong EEG theta rhythm (5-9 Hz) analogous to that of rapid eve movement sleep (REM) sleep. Indeed, pharmacological inhibition of the medial septum ablates theta during halothane anaesthesia,<sup>10</sup> similar to optogenetic silencing<sup>11</sup> and lesioning<sup>12</sup> during REM sleep; however, anaesthetic sensitivity is not altered, suggesting that consciousness is not under the control of the medial septum-hippocampus pathway. GABAergic (gamma-amino butyric acid) agents such as barbiturates, alphaxalone and propofol produce EEG slow waves (<4 Hz) and spindles (single, 1 s oscillatory events in the 11– 16 Hz range), suggesting the recruitment of thalamocortical circuitry. Furthermore, prolonged maintenance of propofol general anaesthesia can result in EEG signals similar to REM

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**Figure 1.** Molecular targets, EEG signatures and spontaneous sleep analogies of major general anaesthetic agents. Many of the primarily GABAergic anaesthetics (the notable exception being benzodiazepines) as well as the  $\alpha_2$ -adrenoceptor agonists produce delta waves and spindles that bear a striking resemblance to those seen during human NREM stages II and III, suggesting a recruitment of thalamocortical networks to produce unconsciousness. Volatile anaesthetics exhibit a promiscuous pharmacology with many molecular targets and a correspondingly high number of proposed neuronal substrates. The EEG of light anaesthesia consists of high theta power, similar to REM sleep, and shares similar neuronal substrates, such as the medial septum-hippocampal pathway. Ketamine and benzo-diazepines have non-overlapping pharmacology, yet both produce a desynchronised wake-like EEG and significantly disrupt cortico-cortical networks.<sup>1</sup>

sleep. Benzodiazepines (e.g. diazepam and midazolam) produce a desynchronised EEG pattern, with little analogy to any spontaneous sleep EEG rhythms and are considered to have a direct cortical action given the predominating alpha (7–14 Hz) in the EEG which has a cortical origin.<sup>13</sup> Ketamine similarly produces a desynchronised EEG and body immobility; however, there is debate as to whether it is a true general anaesthetic. Patients given immobilising doses of ketamine report a dissociative state, consisting of a conscious-like experience and awareness of their environment,<sup>1</sup> suggesting that consciousness is not lost. One intriguing class of drugs is the  $\alpha_2$ -adrenoceptor agonist dexmedetomidine, which acts selectively at this receptor only, presumably via direct inhibition of locus coeruleus (LC) neurones, <sup>14–16</sup> producing a heavy but rousable sedation, similar to that of spontaneous sleep from which subjects may be awoken (unlike hypnosis with other general anaesthetics in which they may not). Furthermore, the EEG of patients undergoing dexmedetomidine sedation is highly analogous to stages II and III of nonrapid eye movement sleep (NREM), with a high predominance of spindles and slow waves.<sup>17</sup> Interestingly, the expression of  $\alpha_{2a}$  adrenoceptors in the brain is highly restricted to the LC, hypothalamus, claustrum and reticular thalamic nucleus (RTN) and layer VI of the cortex,<sup>18</sup> suggesting it may be a useful tool to investigate the convergence of spontaneous sleep and general anaesthetic relevant brain circuits. To date, many molecular targets of general anaesthetics have been identified using both in vitro and in vivo studies<sup>1,19</sup>; however, the underlying neuronal mechanisms remain unclear. The diffuse expression of receptors, particularly GABA<sub>A</sub>, two-pore domain potassium channels (K2P) and n-methyl-d-aspartate (NMDA), throughout the brain means that identification of many of these targets is uninformative as to the changes in brain activity that occur with alterations in consciousness state.<sup>1</sup> Proposed theories for general anaesthetic mechanisms include hypothalamic inhibition,<sup>2–6,20</sup> direct cortical deactivation,<sup>7,21</sup> thalamocortical disruption<sup>9,22,23</sup> and interaction with microtubules.<sup>24</sup>

Several classical sleep-wake regulating hypothalamic areas have been postulated as putative anaesthetic targets, in particular the wake-promoting histamine neurones<sup>2</sup> and the sleep-promoting ventrolateral- and median preoptic (VLPO/MnPO) neurones.<sup>4</sup> The first description of this concept demonstrated a GABAergic modulation of the histaminergic tuberomamillary nucleus (TMN) which altered anaesthetic sensitivity.<sup>5</sup> In this work, it was proposed that wake-promoting histamine neurones are indirectly inhibited by the GABAergic acting drugs muscimol, propofol and pentobarbital. Subsequent work further demonstrated that cellular activity of TMN, but not adrenergic LC, neurones mirrored the anaesthetic sensitivity demonstrated by the  $\beta$ 3 N265-M mouse.<sup>2</sup> This GABA<sub>A</sub> receptor mutation reduces in vivo sensitivity to the hypnotic effects of propofol, as assessed by loss of righting reflex.<sup>25</sup> Additionally, engineering TMN neurones to be sensitive to the sleeppromoting drug zolpidem results in reduced latency and increased duration of sleep<sup>6</sup> suggesting that the TMN may be a common substrate for spontaneous sleep and general anaesthesia. However, removing GABAA receptors from histamine neurones in mice (a genetic manipulation to release inhibition of these cells and render them more excitable) does not alter propofol sensitivity, suggesting that the TMN is not central to general anaesthetic mechanisms.<sup>3</sup>

On the other hand, the sleep-promoting GABAergic neurones of the preoptic hypothalamus play a central role in the flip-flop model of sleep-wake control.<sup>26</sup> Within this area, there are sleep- and wake-active GABAergic neurones, of which only the sleep-active ones are activated by volatile anaesthetics including halothane and isoflurane.<sup>27</sup> Furthermore, genetic ablation of these neurones leads to in vivo resistance to the hypnotic effects of isoflurane whereas their inhibition facilitates arousal.<sup>28</sup> In line with these studies, the VLPO, a small subset of inhibitory neurones located in the anterior hypothalamus, has also been shown to be a key neural substrate for both the sleep homeostatic process and sedation by dexmedetomidine an  $\alpha_2$  adrenergic agonist,<sup>4</sup> a drug which produces electrophysiological EEG slow waves and spindles<sup>17</sup> and behavioural (rousable sedation)<sup>18</sup> states very similar to natural sleep.

Besides these two targets, the hypothalamus contains neuronal populations that are selectively active during sleep and wakefulness. These include melatonin concntrating hormone (MCH), vesicular GABA/glycine transporter (VGAT) and Hcrt/Ox neurones that have been causally involved in sleep<sup>29,30</sup> and arousal,<sup>31-34</sup> respectively. Although the relationship between MCH and Hcrt/ Ox neurones and anaesthesia remains unknown, optogenetic silencing of arousal-promoting GABAergic lateral hypothalamus (LH<sub>VGAT</sub>) neurones is key for sleep stability, sleep homeostasis and deep anaesthesia.<sup>34</sup> Accordingly, optogenetic activation of LH<sub>VGAT</sub> neurones during deep isoflurane anaesthesia (revealed by burst-suppression in the EEG) rapidly induced a sustained cortical arousal and often, a recovery of muscle tone, signalling emergence from anaesthesia and recovery of loss of righting reflex (LORR), which is interpreted as a first step towards regaining of consciousness in animals. This suggests that a proper silencing of these cells is required for stable anaesthesia.

Several of the wake-promoting hypothalamic nuclei have been identified as potential putative anaesthetic targets.<sup>1,2,4–6,14,20</sup> The heterogeneity and complex wiring diagram of hypothalamic neurones have, so far, hampered our understanding of the neurobiological mechanisms underlying brain control of sleep, wake and anaesthesia. Yet, their participation in either the EEG hallmarks or the progressive loss of consciousness associated with general anaesthesia requires further investigation since they project to arousal-promoting cell groups where they may inhibit noradrenergic, serotonergic, cholinergic, histaminergic and hypocretinergic neurones,<sup>35</sup> as previously suggested by the 'reciprocal inhibitory' model of the sleep–wake switch.<sup>36</sup>

## **Beyond hypothalamic circuits**

Many of the sleep-wake regulating hypothalamic nuclei project extensively to the thalamus,<sup>34,37,38</sup> neocortex<sup>6,20,33</sup> and basal forebrain<sup>39</sup>; however, it is yet to be established how hypothalamic perturbation by general anaesthetics results in unconsciousness; *What is their anatomical target?* Answering this question will be crucial to understanding mechanisms of sleep, general anaesthesia and consciousness.

Very few studies have addressed whether either the thalamus or the neocortex are putative anaesthetic targets, which contrasts with their direct implication of cortical EEG patterns of activity. Studies in vitro show that anaesthetics can alter thalamic and cortical neuronal activity, often by increasing potassium conductance,<sup>40,41</sup> but this does not help to explain their behaviour within a network. Both thalamus and cortex show bursting activity during sleep and general anaesthesia rather than being silenced which requires that the neurones are first hyperpolarised.<sup>42,43</sup> Whether this occurs via a direct action on the neurones themselves or as a result of retarded ascending arousal pathways remains unclear.

Human studies using fMRI show that activity of the thalamus is commonly suppressed during general

anaesthesia induced by different agents leading to the theory of a thalamic switch.<sup>44,45</sup> However, others suggest that thalamic activity is merely a read out of cortical activity<sup>7,21</sup> owing to the reciprocal connectivity between thalamus and cortex. A more informative angle of investigation might be to consider how thalamocortical connectivity is perturbed during changes in conscious state.<sup>8</sup> One theory of consciousness formation comes from the large-scale information integration in the neocortex,<sup>46</sup> a process which may be disrupted by general anaesthetics<sup>8</sup> and natural sleep.<sup>47,48</sup> Interestingly, integration across frontal and occipital areas appears to be crucial to consciousness giving rise the parietooccipital 'hotspot' where preferential activation of the EEG occurs during conscious experience.<sup>49</sup> Furthermore, dream recall (considered to be a form of consciousness during sleep) following spontaneous sleep is associated with increased EEG frequency in the same areas.<sup>50</sup>

The role of the thalamus in orchestrating the integration of information in the neocortex is still a matter of debate. Studies in animals have demonstrated that cortical state is determined by thalamic activity<sup>51,52</sup> and that highly localised thalamic activation may result in emergence from anaesthesia.<sup>34,40,53–55</sup> Furthermore, lesions of the central thalamus in humans result in disorders of consciousness.<sup>56–58</sup> Interestingly, activity of the dorsal thalamus, an area involved in multisensory integration, 59,60 is disrupted in Schizophrenia where conscious perception is often perturbed.<sup>61,62</sup> However, extensive lateral thalamic lesions in rats do not result in unconsciousness, whereas lesioning of the basal forebrain produces coma.<sup>63</sup> While this may dismiss a role for thalamus in conscious control, the lateral sensory thalamus only has control of small localised cortical regions and does not receive ascending arousal connections.<sup>60,64</sup> Furthermore, sensory information relayed by the sensory thalamus may reach the primary sensory cortex during all vigilance states,<sup>65</sup> suggesting that gating of sensory information during unconsciousness occurs elsewhere in the thalamus.

The thalamus is a functionally heterogeneous region<sup>60,66</sup> suggesting that distinct thalamic nuclei may be important for the regulation of consciousness.<sup>23,40,57</sup> Sensory evoked potentials can be elicited in primary sensory cortices during natural sleep,<sup>65</sup> anaesthesia<sup>67,68</sup> and vegetative state,<sup>69</sup> suggesting that connectivity between sensory thalamus and cortex is not disrupted during unconsciousness. Data from animals<sup>23,67,70,71</sup> and humans<sup>22,68,72–74</sup> indicate that disruption of higher order, but not primary, thalamocortical connectivity is responsible for loss of consciousness observed in both general anaesthesia and natural sleep. Furthermore, the higher order and midline thalamus have been shown to integrate sensory information in the cortex  $^{66,75-77}$  as well as receiving multiple ascending arousal inputs,78-80 which the lateral sensory thalamus does not. In accordance with this, activation of the midline thalamus increases awareness in coma patients<sup>56</sup> and can result in anaesthetic emergence in animals.40,53

Taken together, these data implicate thalamocortical circuitry in the control of consciousness and sleep. It remains to be determined how this circuitry is modulated to switch between wakefulness and spontaneous sleep or general anaesthesia.

## Perspectives

To date, there is a considerable volume of observational work on the mechanisms of natural sleep and general anaesthesia. Most of these have identified common pathways in the hypothalamus and pons where targeting of regions is relatively straight forward. These identified targets are further consistent with the varying degree of autonomic disturbance produced by different general anaesthetics. Perturbational approaches to determine the mechanisms of consciousness are still in their infancy. Important insights have been gleamed from altering molecular expression in hypothalamic nuclei in animal models; however, this work is yet to be extended to investigate the neural substrates at the thalamic and cortical level which are necessary for consciousness. Furthermore, most of the work has focused on altering anaesthetic sensitivity by targeting wake-promoting neurones. Experimental wakepromoting circuit evoked emergence from anaesthesia does not implicate these as putative anaesthetic targets. In that sense, it would be interesting to investigate whether sleeppromoting systems either prolong, deepen or hasten the onset of general anaesthesia. Indeed, many anaesthetics exhibit hysteresis with regard to induction and recovery,<sup>81</sup> suggesting that different mechanisms are responsible for each process. A greater understanding of the circuit mechanisms involved in modulation of the thalamus and cortex is needed to design experiments to interrogate the thalamocortical networks underpinning sleep, general anaesthesia and consciousness.

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