

# 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 sleep-mediating 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 eye 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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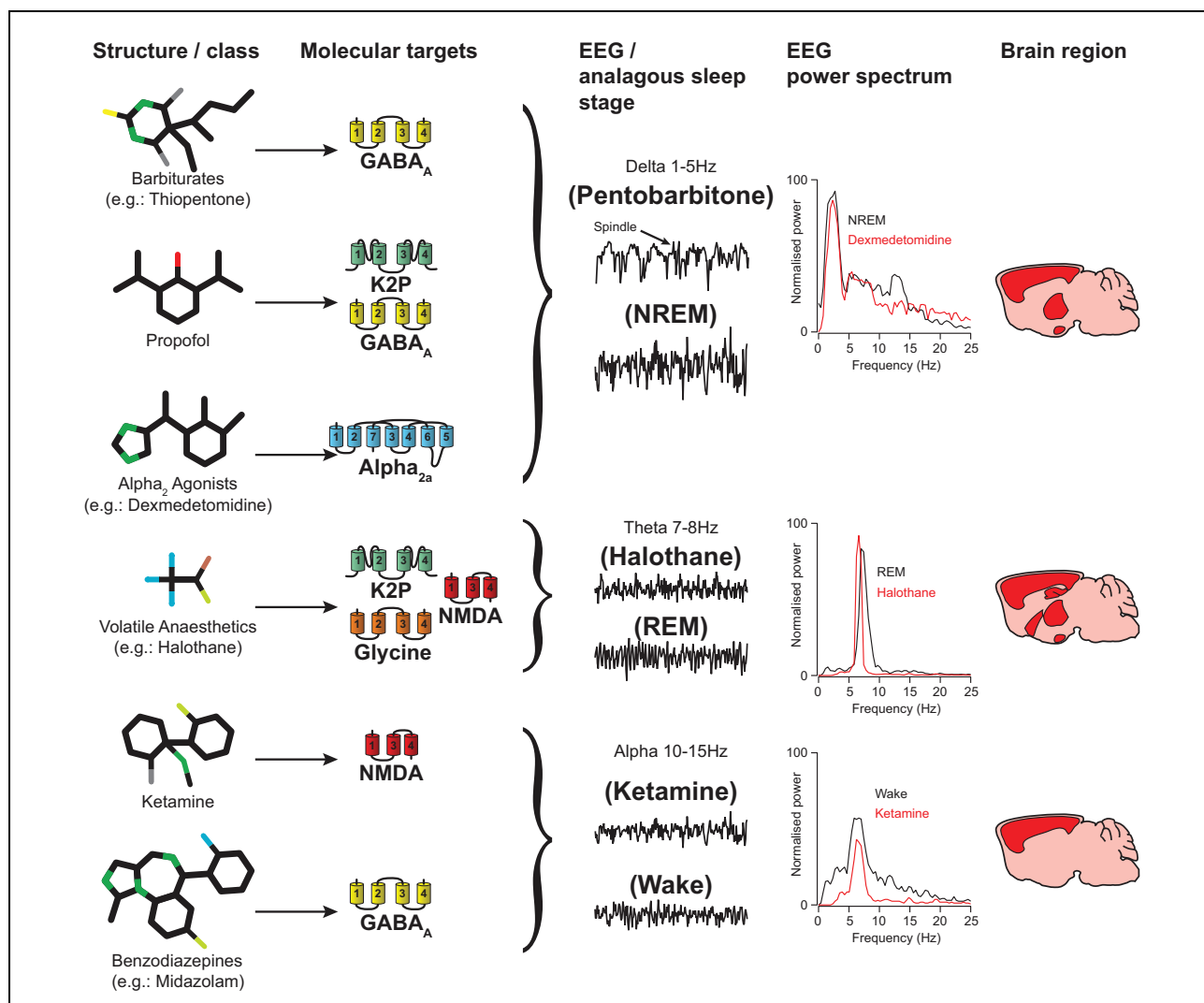
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**Figure 1.** Molecular targets, EEG signatures and spontaneous sleep analogies of major general anaesthetic agents. Many of the primarily GABAergic anaesthetics (the notable exception being benzodiazepines) as well as the  $\alpha_2$ -adrenoceptor 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 benzodiazepines 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 non-rapid 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 tuberomammillary 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 sleep-promoting 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 GABA<sub>A</sub> 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

concentrating 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 hypocretineric 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 parieto-occipital '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,<sup>59,60</sup> 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<sup>66,75–77</sup> as well as receiving multiple ascending arousal inputs,<sup>78–80</sup> 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.<sup>40,53</sup>

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 gleaned 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 wake-promoting circuit evoked emergence from anaesthesia does not implicate these as putative anaesthetic targets. In that sense, it would be interesting to investigate whether sleep-promoting 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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## References

1. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci* 2008; 9(5): 370–386.
2. Zecharia AY, Nelson LE, Gent TC, et al. The involvement of hypothalamic sleep pathways in general anesthesia: testing

- the hypothesis using the GABAA receptor beta3N265 M knock-in mouse. *J Neurosci* 2009; 29(7): 2177–2187.
3. Zecharia AY, Yu X, Gotz T, et al. GABAergic inhibition of histaminergic neurons regulates active waking but not the sleep-wake switch or propofol-induced loss of consciousness. *J Neurosci* 2012; 32(38): 13062–13075.
  4. Zhang Z, Ferretti V, Guntan I, et al. Neuronal ensembles sufficient for recovery sleep and the sedative actions of alpha2 adrenergic agonists. *Nat Neurosci* 2015; 18(4): 553–561.
  5. Nelson LE, Guo TZ, Lu J, et al. The sedative component of anesthesia is mediated by GABA(A) receptors in an endogenous sleep pathway. *Nat Neurosci* 2002; 5(10): 979–984.
  6. Uygun DS, Ye Z, Zecharia AY, et al. Bottom-up versus top-down induction of sleep by zolpidem acting on histaminergic and neocortex neurons. *J Neurosci* 2016; 36(44): 11171–11184.
  7. Alkire MT, Hudetz AG and Tononi G. Consciousness and anesthesia. *Science* 2008; 322(5903): 876–880.
  8. Hudetz AG. General anesthesia and human brain connectivity. *Brain Connect* 2012; 2(6): 291–302.
  9. Brown EN, Lydic R and Schiff ND. General anesthesia, sleep, and coma. *N Engl J Med* 2010; 363(27): 2638–2650.
  10. Pang DS, Robledo CJ, Carr DR, et al. An unexpected role for TASK-3 potassium channels in network oscillations with implications for sleep mechanisms and anesthetic action. *Proc Natl Acad Sci U S A* 2009; 106(41): 17546–17551.
  11. Boyce R, Glasgow SD, Williams S, et al. Causal evidence for the role of REM sleep theta rhythm in contextual memory consolidation. *Science* 2016; 352(6287): 812–816.
  12. Lawson VH and Bland BH. The role of the septohippocampal pathway in the regulation of hippocampal field activity and behavior: analysis by the intraseptal microinfusion of carbachol, atropine, and procaine. *Exp Neurol* 1993; 120(1): 132–144.
  13. Ferrarelli F, Massimini M, Sarasso S, et al. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. *Proc Natl Acad Sci U S A* 2010; 107(6): 2681–2686.
  14. Correa-Sales C, Nacif-Coelho C, Reid K, et al. Inhibition of adenylate cyclase in the locus coeruleus mediates the hypnotic response to an alpha 2 agonist in the rat. *J Pharmacol Exp Ther* 1992; 263(3): 1046–1049.
  15. Correa-Sales C, Rabin BC and Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992; 76(6): 948–952.
  16. Correa-Sales C, Reid K and Maze M. Pertussis toxin-mediated ribosylation of G proteins blocks the hypnotic response to an alpha 2-agonist in the locus coeruleus of the rat. *Pharmacol Biochem Behav* 1992; 43(3): 723–727.
  17. Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. *Acta Anaesthesiol Scand* 2008; 52(2): 289–294.
  18. Gelegen C, Gent TC, Ferretti V, et al. Staying awake – a genetic region that hinders alpha2 adrenergic receptor agonist-induced sleep. *Eur J Neurosci* 2014; 40(1): 2311–2319.
  19. Franks NP and Lieb WR. Molecular and cellular mechanisms of general anaesthesia. *Nature* 1994; 367(6464): 607–614.
  20. Yu X, Ye Z, Houston CM, et al. Wakefulness is governed by GABA and histamine cotransmission. *Neuron* 2015; 87(1): 164–178.
  21. Velly LJ, Rey MF, Bruder NJ, et al. Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. *Anesthesiology* 2007; 107(2): 202–212.
  22. Akeju O, Loggia ML, Catana C, et al. Disruption of thalamic functional connectivity is a neural correlate of dexmedetomidine-induced unconsciousness. *Elife* 2014; 3: e04499.
  23. Baker R, Gent TC, Yang Q, et al. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. *J Neurosci* 2014; 34(40): 13326–13335.
  24. Craddock TJ, Hameroff SR, Ayoub AT, et al. Anesthetics act in quantum channels in brain microtubules to prevent consciousness. *Curr Top Med Chem* 2015; 15(6): 523–533.
  25. Jurd R, Arras M, Lambert S, et al. General anesthetic actions in vivo strongly attenuated by a point mutation in the GABA(A) receptor beta3 subunit. *FASEB J* 2003; 17(2): 250–252.
  26. Saper CB, Fuller PM, Pedersen NP, et al. Sleep state switching. *Neuron* 2010; 68(6): 1023–1042.
  27. Moore JT, Chen J, Han B, et al. Direct activation of sleep-promoting VLPO neurons by volatile anesthetics contributes to anesthetic hypnosis. *Curr Biol* 2012; 22(21): 2008–2016.
  28. McCarren HS, Chalifoux MR, Han B, et al. Alpha2-Adrenergic stimulation of the ventrolateral preoptic nucleus destabilizes the anesthetic state. *J Neurosci* 2014; 34(49): 16385–16396.
  29. Jegu S, Glasgow SD, Herrera CG, et al. Optogenetic identification of a rapid eye movement sleep modulatory circuit in the hypothalamus. *Nat Neurosci* 2013; 16(11): 1637–1643.
  30. Konadhode RR, Pelluru D and Shiromani PJ. Neurons containing orexin or melanin concentrating hormone reciprocally regulate wake and sleep. *Front Syst Neurosci* 2014; 8: 244.
  31. Adamantidis AR, Zhang F, Aravanis AM, et al. Neural substrates of awakening probed with optogenetic control of hypocretin neurons. *Nature* 2007; 450(7168): 420–U9.
  32. Carter ME, Adamantidis A, Ohtsu H, et al. Sleep homeostasis modulates hypocretin-mediated sleep-to-wake transitions. *J Neurosci* 2009; 29(35): 10939–10949.
  33. Carter ME, Yizhar O, Chikahisa S, et al. Tuning arousal with optogenetic modulation of locus coeruleus neurons. *Nat Neurosci* 2010; 13(12): 1526–1533.
  34. Herrera CG, Cadavieco MC, Jegu S, et al. Hypothalamic feed-forward inhibition of thalamocortical network controls arousal and consciousness. *Nat Neurosci* 2016; 19(2): 290–298.
  35. Suntsova N, Guzman-Marin R, Kumar S, et al. The median preoptic nucleus reciprocally modulates activity of arousal-

- related and sleep-related neurons in the perifornical lateral hypothalamus. *J Neurosci* 2007; 27(7): 1616–1630.
36. Pace-Schott EF and Hobson JA. The neurobiology of sleep: genetics, cellular physiology and subcortical networks. *Nat Rev Neurosci* 2002; 3(8): 591–605.
  37. Peyron C and Kilduff TS. Mapping the hypocretin/orexin neuronal system: an unexpectedly productive journey. *J Neurosci* 2017; 37(9): 2268–2272.
  38. Bittencourt JC, Presse F, Arias C, et al. The melanin-concentrating hormone system of the rat brain: an immunohistochemical and hybridization histochemical characterization. *J Comp Neurol* 1992; 319(2): 218–245.
  39. Anaclet C, Pedersen NP, Ferrari LL, et al. Basal forebrain control of wakefulness and cortical rhythms. *Nat Commun* 2015; 6: 8744.
  40. Lioudyno MI, Birch AM, Tanaka BS, et al. Shaker-related potassium channels in the central medial nucleus of the thalamus are important molecular targets for arousal suppression by volatile general anesthetics. *J Neurosci* 2013; 33(41): 16310–16322.
  41. Jhangiani-Jashanmal I, Yamamoto R, Gungor NZ, et al. Electroresponsive properties of rat central medial thalamic neurons. *J Neurophysiol* 2016; 115(3): 1533–1541.
  42. Steriade M, Nunez A and Amzica F. Intracellular analysis of relations between the slow (< 1 Hz) neocortical oscillation and other sleep rhythms of the electroencephalogram. *J Neurosci* 1993; 13(8): 3266–3283.
  43. McCormick DA, McGinley MJ and Salkoff DB. Brain state dependent activity in the cortex and thalamus. *Curr Opin Neurobiol* 2015; 31: 133–140.
  44. Alkire MT, Haier RJ and Fallon JH. Toward a unified theory of narcosis: brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. *Conscious Cogn* 2000; 9(3): 370–386.
  45. Bonhomme V, Fiset P, Meuret P, et al. Propofol anesthesia and cerebral blood flow changes elicited by vibrotactile stimulation: a positron emission tomography study. *J Neurophysiol* 2001; 85(3): 1299–1308.
  46. Tononi G, Boly M, Massimini M, et al. Integrated information theory: from consciousness to its physical substrate. *Nat Rev Neurosci* 2016; 17: 450–461.
  47. Massimini M, Ferrarelli F, Huber R, et al. Breakdown of cortical effective connectivity during sleep. *Science* 2005; 309(5744): 2228–2232.
  48. Massimini M, Ferrarelli F, Sarasso S, et al. Cortical mechanisms of loss of consciousness: insight from TMS/EEG studies. *Arch Ital Biol* 2012; 150(2–3): 44–55.
  49. Siclari F, Bernardi G, Riedner BA, et al. Two distinct synchronization processes in the transition to sleep: a high-density electroencephalographic study. *Sleep* 2014; 37(10): 1621–1637.
  50. Siclari F, Baird B, Perogamvros L, et al. The neural correlates of dreaming. *Nat Neurosci* 2017; 20(6): 872–878.
  51. Poulet JF and Petersen CC. Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. *Nature* 2008; 454(7206): 881–885.
  52. Poulet JF, Fernandez LM, Crochet S, et al. Thalamic control of cortical states. *Nat Neurosci* 2012; 15(3): 370–372.
  53. Alkire MT, McReynolds JR, Hahn EL, et al. Thalamic microinjection of nicotine reverses sevoflurane-induced loss of righting reflex in the rat. *Anesthesiology* 2007; 107(2): 264–272.
  54. Alkire MT, Asher CD, Franciscus AM, et al. Thalamic microinfusion of antibody to a voltage-gated potassium channel restores consciousness during anesthesia. *Anesthesiology* 2009; 110(4): 766–773.
  55. Liu J, Lee HJ, Weitz AJ, et al. Frequency-selective control of cortical and subcortical networks by central thalamus. *Elife* 2015; 4: e09215.
  56. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. *Nature* 2007; 448(7153): 600–603.
  57. Schiff ND and Fins JJ. Brain death and disorders of consciousness. *Curr Biol* 2016; 26(13): R572–R576.
  58. Langsjo JW, Lehtimäki K, Ruohonen J, et al. Critical neural targets for (the level of) human consciousness: arousal arrest and unconsciousness after sumatriptan administration. *Brain Inj* 2016; 30(13–14): 1731–1736.
  59. Viaene AN, Petrof I and Sherman SM. Properties of the thalamic projection from the posterior medial nucleus to primary and secondary somatosensory cortices in the mouse. *Proc Natl Acad Sci U S A* 2011; 108(44): 18156–18161.
  60. Sherman SM. Thalamus plays a central role in ongoing cortical functioning. *Nat Neurosci* 2016; 16(4): 533–541.
  61. Uhlhaas PJ and Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 2010; 11(2): 100–113.
  62. Parnaudeau S, O'Neill PK, Bolkan SS, et al. Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. *Neuron* 2013; 77(6): 1151–1162.
  63. Fuller PM, Sherman D, Pedersen NP, et al. Reassessment of the structural basis of the ascending arousal system. *J Comp Neurol* 2011; 519(5): 933–956.
  64. Phillipson OT and Bohn MC. C1-3 adrenergic medullary neurones project to the paraventricular thalamic nucleus in the rat. *Neurosci Lett* 1994; 176(1): 67–70.
  65. Nir Y, Vyazovskiy VV, Cirelli C, et al. Auditory responses and stimulus-specific adaptation in rat auditory cortex are preserved across NREM and REM sleep. *Cereb Cortex* 2015; 25(5): 1362–1378.
  66. Saalmann YB. Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. *Front Syst Neurosci* 2014; 8: 83.
  67. Mease RA, Metz M and Groh A. Cortical sensory responses are enhanced by the higher-order thalamus. *Cell Rep* 2015; 14(2): 208–215.
  68. Liu X, Lauer KK, Ward BD, et al. Propofol disrupts functional interactions between sensory and high-order processing of auditory verbal memory. *Hum Brain Mapp* 2012; 33(10): 2487–2498.
  69. Laureys S, Faymonville ME, Degueldre C, et al. Auditory processing in the vegetative state. *Brain* 2000; 123(Pt 8): 1589–1601.

70. Miller JW and Ferrendelli JA. The central medial nucleus: thalamic site of seizure regulation. *Brain Res* 1990; 508(2): 297–300.
71. Van der Werf YD, Witter MP and Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Brain Res Rev* 2002; 39(2–3): 107–140.
72. Martuzzi R, Ramani R, Qiu M, et al. Functional connectivity and alterations in baseline brain state in humans. *Neuroimage* 2010; 49(1): 823–834.
73. Liu X, Li R, Yang Z, et al. Differential effect of isoflurane, medetomidine, and urethane on BOLD responses to acute levo-tetrahydropalmatine in the rat. *Magn Reson Med* 2012; 68(2): 552–559.
74. Bassetti C, Mathis J, Gugger M, et al. Hypersomnia following paramedian thalamic stroke: a report of 12 patients. *Ann Neurol* 1996; 39(4): 471–480.
75. Saalmann YB, Pinsk MA, Wang L, et al. The pulvinar regulates information transmission between cortical areas based on attention demands. *Science* 2012; 337(6095): 753–756.
76. Laureys S, Faymonville ME, Luxen A, et al. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet* 2000; 355(9217): 1790–1791.
77. Kinomura S, Larsson J, Gulyas B, et al. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. *Science* 1996; 271(5248): 512–515.
78. Krout KE, Belzer RE and Loewy AD. Brainstem projections to midline and intralaminar thalamic nuclei of the rat. *J Comp Neurol* 2002; 448(1): 53–101.
79. Jones BE and Yang TZ. The efferent projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. *J Comp Neurol* 1985; 242(1): 56–92.
80. Pare D, Smith Y, Parent A, et al. Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic nuclei. *Neuroscience* 1988; 25(1): 69–86.
81. Friedman EB, Sun Y, Moore JT, et al. A conserved behavioral state barrier impedes transitions between anesthetic-induced unconsciousness and wakefulness: evidence for neural inertia. *PLoS One* 2010; 5(7): e11903.