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EDITORIAL II

Sleep neurobiology: relevance for mechanistic studies of anaesthesia

The July 1993 issue of *British Journal of Anaesthesia* presented state of the art contributions from a symposium on the cellular and molecular aspects of anaesthesia. The editorial introduction expressed the hope that these proceedings would encourage multidisciplinary studies and stimulate interest in the mechanisms by which anaesthetics cause altered states of consciousness [1]. The purpose of this communication is to respond to the call for multidisciplinary approaches by highlighting recent advances in sleep neurobiology that are of special relevance for anaesthesia. A corollary of the thesis advanced by Halsey, Prys Roberts and Strunin [1] is that cellular and molecular level studies of naturally occurring states of consciousness may prove to be important in understanding anaesthetically induced states of consciousness.

Mechanistic studies of natural sleep, in common with those of anaesthesia, are a very recent development. Only 40 years have passed since the discovery of rapid eye movement (REM) sleep. In 1953, REM sleep was first identified as an electrographically unique state of consciousness, characterized in humans by reports of dreaming mentation and altered respiratory control [2]. As a special state of consciousness, REM sleep remained underappreciated until it was paired with two contiguous advances. One was Moruzzi and Magoun's [3] earlier finding of an arousal-promoting brain stem network: the ascending reticular activating system. A second key finding was the discovery by Jouvet [4] that the pontine reticular formation played a key role in REM sleep generation. These seminal discoveries promoted the experimental study of sleep as a state of consciousness by demonstrating that sleep is not simply the loss of wakefulness [5]. Natural sleep, in common with states of anaesthesia, is actively generated by the brain. Thus neurobiological studies of natural sleep and anaesthesia have a shared interest in elucidating the brain mechanisms generating complex states of consciousness.

States defined by traits. Mechanistic studies of anaesthesia and natural sleep are united by the need to examine the classic but troublesome mind–body problem. For practical purposes, this problem is often expressed as the need to formulate operational definitions for states of consciousness. The concept of *state* has commonly been used to describe the dynamic properties of physicochemical systems. General theories of oxidative phosphorylation, for example, have described the steps from oxidation to reduction displayed by mitochondrial enzymes as different reaction states [6]. Binary computational circuits are characteristically dynamic and unique combinations of zeros and ones describe the state of a central processing unit. These and other similarities between silicon-based computational processing and neuronally based information processing led Ashby [7] to define a brain state as the collection of physiological variables measured at some point in time. Thus a constellation of physiological and behavioural traits may define a state of consciousness.

Dissociated states of consciousness. The foregoing state definition is a clinically useful construct for studies of both natural sleep [8] and anaesthesia [9]. The disruption of normally co-ordinated physiological traits is common in anaesthesia and dissociated states represent an entire group of sleep disorders [10]. For both natural sleep and anaesthesia, dissociated states are characterized by a mixture of physiological and behavioural traits appropriate to one state of consciousness but not to another. For example, spinal alpha motor neurones are normally hyperpolarized during REM sleep resulting in muscle atonia which ends before the onset of wakefulness. In sleep paralysis, commonly experienced by narcoleptic patients, wakefulness precedes the resumption of motor control and affected individuals experience intervals of wakefulness while being unable to move [11]. Conversely, failure of normal motor inhibitory processes during REM sleep is a recognized disorder in which sleeping patients may ambulate, talk and express complex motor acts. This REM sleep behaviour disorder is characterized by seemingly purposive behaviours carried out while asleep and commonly results in injuries to the patient [12]. Dissociated states of consciousness also are a serious concern for clinical anaesthesia. Numerous dissociated states have been documented during which a patient appears to be anaesthetized and surgery proceeds on a paralysed but otherwise conscious patient [13]. Therefore, for both natural sleep and anaesthesia, it is important to understand the brain mechanisms by which a diverse collection of autonomic and behavioural traits are generated and orchestrated into a more or less coherent state.

Towards a unifying approach to state control. Efforts to understand how anaesthetic agents interact with lipid and protein components of neuronal membranes represent exciting areas of anaesthesia research. Elucidating the *sites* of anaesthetic action, however, is likely to offer an incomplete understanding for all the *mechanisms* of anaesthetic action. The elegance of site-directed research derives, in part, from the ability to isolate and experimentally manipulate subcellular components. In contrast, experimental approaches directed towards understanding the mechanisms by which anaesthetics block pain, diminish respiration or eliminate wakefulness include complex neuronal networks. Broad research strategies recognize the importance of understanding both site and mechanism of anaesthetic action and that there is no single mechanism by which all anaesthetics produce their effects [14].

Many pieces of evidence demonstrate that states of consciousness and state-dependent changes in autonomic physiology are generated by anatomically distributed neuronal networks [5, 15]. Throughout

these networks, neurochemically identified cell types and postsynaptic receptor systems are distributed differentially. This specificity of neuronal organization helps in understanding how different anaesthetic agents can exert differential effects on neuronal function. This has led to the suggestion that anaesthetic agents "set in train an integrated series of events which may explain one or more of the facets observed in clinical practice" [16]. Thus an event such as anaesthesia-induced respiratory depression is likely to result from both sites of anaesthetic action and altered mechanisms in neuronal networks regulating breathing.

REM sleep has been observed in all placental, terrestrial mammals studied to date. The ubiquity of REM sleep derives from the central nervous system homology present across species. Thus it is highly probable that neuronal mechanisms which have evolved for regulating naturally occurring states are preferentially involved in generating some traits characteristic of anaesthetic-induced states. REM sleep and anaesthesia share some remarkable similarities. Both states are characterized by motor hypotonia, disruptions in temperature regulation, changes in EEG amplitude and frequency, disconjugate eye movements, altered mentation, diminished sensory processing and respiratory depression. Angel [2] cautioned that it is necessary to study events at the single-cell level in order to appreciate the differential effects of anaesthetics. Below are described some recent cellular studies which have shown that cholinergic and cholinoceptive brain stem reticular mechanisms interact significantly with states of REM sleep and anaesthesia.

Cholinergic control of consciousness. It has been appreciated for more than 25 years that direct application of microgram quantities of cholinergic agonists into the medial pontine reticular formation of intact, unanaesthetized animals causes a REM sleep-like state (reviewed in [17]). This REM sleep-like state is dose-dependent, blocked by atropine and site-specific within the medial pontine reticular formation. This pharmacological model supports the view that REM sleep is regulated, at least in part, by muscarinic cholinergic receptors of the non-M1 variety, localized within the medial pontine reticular formation [5]. Some of these same cholinergic mechanisms have been shown recently to contribute to state-dependent respiratory depression [18, 19]. As described below, we have been using this cholinergic model of REM sleep to investigate the hypothesis that cholinergic reticular mechanisms also play a role in regulating some anaesthetic states.

Patients receiving opioids report feeling sleepy but their drugs are well known to inhibit the REM phase of sleep [20]. As REM sleep is homeostatically regulated, opioid-induced REM sleep inhibition is followed by a rebound increase in REM sleep when the drugs are withdrawn [21]. In patients with obstructive sleep apnoea, a rebound increase in REM sleep may be associated with increased episodes of apnoea and potentially fatal respiratory complications [22, 23]. The brain mechanisms mediating opioid-induced REM sleep inhibition are poorly understood. It was of interest to learn from animal studies that injecting minute doses of morphine into regions of the medial pontine reticular formation known to be involved in REM sleep generation, significantly inhibited REM sleep and increased the number of episodes of apnoea [24]. This inhibition of opioid-induced REM sleep was dose-dependent and blocked by naloxone. More recently, animal studies using *in vivo* microdialysis and high pressure liquid chromatography (HPLC) have shown that systemically administered morphine decreased significantly release of acetylcholine in the medial pontine reticular formation [25]. As pontine cholinergic neurotransmission has been shown to play a role in both REM sleep generation and state-dependent respiratory depression, these experiments identified a brain region and a neurotransmitter which contribute to REM sleep inhibition and respiratory depression caused by morphine.

We wondered if the results obtained with morphine would be observed with volatile anaesthetics. Griffiths and Norman [26] noted that "few studies of the effects of anaesthetic agents on release of acetylcholine have been performed." We postulated that the inhibitory actions on acetylcholine release in the medial pontine reticular formation would be observed also in the presence of halothane. Microdialysis and HPLC have revolutionized neurochemistry [27] making it possible to dialyse specific brain regions *in vivo* during defined states of consciousness. We have used these techniques to examine neurotransmitter release at specific MAC values and during subsequent wakefulness. The results revealed that 1 MAC of halothane caused statistically significant reductions in pontine acetylcholine release compared with release observed in the same brain regions during wakefulness [28].

The results of these animal studies also point to an interesting relationship between MAC of halothane and simultaneous measures of the cortical electroencephalogram (EEG). Before describing those results, it should be acknowledged that use of the EEG as an index of anaesthesia is not without controversy. At least four scholarly and provocative papers have questioned recently the ability to cause or measure states of anaesthesia [9, 13, 29, 30]. While we are aware of the complexities of judging anaesthetic state based on EEG or other traits, the recent microdialysis studies found that 1 MAC of halothane always caused numerous EEG spindles. Interestingly, these halothane spindles were indistinguishable from natural sleep spindles. During halothane anaesthesia, noxious stimuli abolished these EEG spindles, just as somatosensory input causes EEG desynchronization and arousal from natural sleep. These quantitative and qualitative similarities in the EEG suggest that halothane spindles and natural sleep spindles may be generated by the same thalamocortical mechanisms [28].

These studies have demonstrated that cholinergic neurotransmission in the pontine reticular formation is significantly altered by morphine, halothane and REM sleep. Electrophysiological studies have shown that these same cholinergic reticular mechanisms can decrease the discharge of parabrachial respiratory neurones [31]. In combination, these results are

consistent with the view that cholinergic neurotransmission in the pontine reticular formation may generate some of the physiological traits associated with halothane and morphine anaesthesia. If this working hypothesis is supported by subsequent data, it should lead to a potentially important conclusion, notably the concept that brain stem mechanisms known to be involved in generation of naturally occurring sleep play a key role in generating some of the physiological traits observed during some states of anaesthesia. It remains to be seen if the neurobiology of natural sleep and anaesthesia will move towards a unified theory of state control.

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REFERENCES

1. Halsey MJ, Prys Roberts C, Strunin L. Receptors and transmembrane signalling: cellular and molecular aspects of anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 1.
2. Aserensky E, Kleitman N. Regularly occurring periods of eye motility and concomitant phenomena during sleep. *Science* 1953; **118**: 273–274.
3. Moruzzi G, Magoun HW. Brainstem reticular formation and activation of the EEG. *Electroencephalography and Clinical Neurophysiology* 1949; **1**: 455–473.
4. Jouvet M. Recherches sur les structures nerveuses et les mecanismes responsables des differentes phases du sommeil physiologique. *Archives Italiennes de Biologie* 1962; **100**: 125–206.
5. Steriade M, McCarley RW. *Brainstem Control of Wakefulness and Sleep*. London: Plenum Press, 1990.
6. Chance B, Williams GR. Respiratory enzymes in oxidative phosphorylation. *Journal of Biological Chemistry* 1955; **217**: 409–427.
7. Ashby WR. *Design for a Brain*. London: Chapman and Hall, 1960.
8. Hobson JA. Cellular neurophysiology and sleep research. In: Chase M, ed. *The Sleeping Brain*. Los Angeles: UCLA Brain Information Service, 1972; 59–92.
9. Prys Roberts C. Anaesthesia: A practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.
10. Mahowald MW, Schenck CH. Dissociated states of wakefulness and sleep. *Neurology* 1992; **42**: 44–52.
11. Hishikawa Y. Sleep paralysis. In: Guilleminault C, Dement WC, Passouant P, eds. *Narcolepsy*. New York: Spectrum, 1975; 97–124.
12. Mahowald MW, Schenck CH. REM sleep behavior disorder. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia: Saunders, 1989; 389–401.
13. Kulli J, Koch C. Does anaesthesia cause loss of consciousness? *Trends in Neuroscience* 1991; **14**: 6–10.
14. Richards CD. In search of the mechanisms of anaesthesia. *Trends in Neuroscience* 1980; **3**: 9–13.
15. Lydic R, Biebuyck JF. *The Clinical Physiology of Sleep*. Bethesda: The American Physiological Society, 1988.
16. Angel A. Central neuronal pathways and the process of anaesthesia. *British Journal of Anaesthesia* 1993; **71**: 148–163.
17. Baghdoyan HA, Spotts JL, Snider SG. Simultaneous pontine and basal forebrain microinjections of carbachol suppress REM sleep. *Journal of Neuroscience* 1993; **13**: 227–240.
18. Lydic R, Baghdoyan HA. Respiratory depression and increased acetylcholine release in the medial pontine reticular formation caused by pedunculopontine tegmental nucleus stimulation. *American Journal of Physiology* 1993; **264**: R544–R554.
19. Lydic R, Baghdoyan HA. The neurobiology of REM sleep. In: Saunders NA, Sullivan C, eds. *Sleep and Breathing*, 2nd Edn, Vol. 21 of *Lung Biology in Health and Disease* (Lenfant C ed). New York: Marcel Dekker, 1994; 47–78.
20. Kay DC, Eisenstein RB, Jasinski DR. Morphine effects on human REM state, waking state, and NREM sleep. *Psychopharmacologia* 1969; **14**: 404–416.
21. Knill RL, Moote CA, Skinner MI, Rose EA. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61.
22. Entwistle MD, Roe PG, Sapsford DJ, Berrisford RG, Jones JG. Patterns of oxygenation after thoracotomy. *British Journal Anaesthesia* 1991; **67**: 704–711.
23. VanDercar DJ, Martinez AP, De Lisser EA. Sleep apnea syndrome: A potential contraindication for patient controlled analgesia. *Anesthesiology* 1991; **74**: 623–624.
24. Keifer JC, Baghdoyan HA, Lydic R. Sleep disruption and increased apneas after pontine microinjection of morphine. *Anesthesiology* 1992; **77**: 973–983.
25. Lydic R, Keifer JC, Baghdoyan HA, Becker L. Microdialysis of the pontine reticular formation reveals inhibition of acetylcholine release by morphine. *Anesthesiology* 1993; **79**: 1003–1012.
26. Griffiths R, Norman RI. Effect of anaesthetics on uptake, synthesis and release of transmitters. *British Journal of Anaesthesia* 1993; **71**: 96–107.
27. Robinson TE, Justice JB. *Microdialysis in the Neurosciences*. London: Elsevier, 1990.
28. Keifer JC, Baghdoyan HA, Becker L, Lydic R. Halothane anaesthesia causes decreased acetylcholine release in the pontine reticular formation and increased EEG spindles. *NeuroReport* 1994; **5**: 577–580.
29. Hug CG. Does opioid "anaesthesia" exist? *Anesthesiology* 1990; **73**: 1–4.
30. Kissin I. General anesthetic action: An obsolete notion? *Anesthesia and Analgesia* 1993; **76**: 215–218.
31. Gilbert KA, Lydic R. Pontine cholinergic mechanisms cause state-dependent depression in the discharge of parabrachial respiratory neurons. *American Journal of Physiology* 1994; **266**: R136–150.