Research on anesthesia, consciousness or both? Understanding our anesthetic drugs and defining the neural substrate

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ANESTHESIOLOGISTS are in a unique situation. We are striving to understand the complex nature of anesthesia, but the targets for the drugs we use are still poorly defined. Based on an impressive amount of empirical knowledge and decades of careful clinical research, we are now able to modulate very precisely the state of consciousness of our patient, but we cannot yet provide a comprehensive, scientific explanation of the neural processes involved. However, by looking at how anesthetic drugs effect neural targets, anesthesia researchers help to refine the understanding of how central nervous system (CNS) networks support cognitive functions.

Consciousness is a complex state that still escapes a universal definition. Conceptually, it can have various meanings whether it is considered from the angle of neurology, psychology, philosophy or religion. In a recent review, Zeman¹ was suggesting three definitions for consciousness.

First, consciousness can be seen as “the waking state”: an ability to perceive, interact and communicate with the environment and others in an integrated manner. Interestingly, consciousness in that context changes along a scale ranging from complete wakefulness to coma, a concept that parallels our definition of anesthetic depth.

A second definition relates consciousness to experience as the behavioural expression of our normal waking state and relates to a more subjective dimension of experience. It calls for how it feels to be ourselves, and puts the conscious experience in the context of the feeling of the moment but also links our sense of being to our past experience through the complex interplay of cognitive processes like memory, emotion, thought, language and action planning.

Finally, consciousness can be defined in a broader sense as synonymous with the mind itself. It is a fully integrated view on our capacity to perceive and process information to end up with a final mental state. For example, we are conscious that the health system in Canada is underfunded.

Our knowledge of the neural organization needed to fully sustain the conscious state has evolved in the past decades, but is still very parcellar. The search for neural correlates of consciousness has allowed to identify a network of structures in the CNS that is absolutely essential for the existence of a conscious state. The studies made by Von Economo,² Bremer³ and the pioneering work of Moruzzi and Magoun⁴ gave birth to the concept of the ascending reticular activating system, but we now know that consciousness does not reside in one single site in the CNS. The importance of structures like cholinergic nuclei of the upper brainstem and basal forebrain, noradrenergic nuclei of the locus coeruleus, histaminergic nuclei of the hypothalamus and dopaminergic and serotonergic pathways arising from the brainstem have been shown (for a review of this topic see Steriade *et al.*⁵). These all project to the thalamus where the afferent information is relayed to cortical structures.

Interestingly, in his review, Zeman uses a disclaimer stating that he uses consciousness and awareness synonymously. This is often how we anesthesiologists refer to consciousness, being interested in the practical aspects of patient care and concerned about the possibility that a patient might be aware during surgical procedures. However, in our practice, we use anesthetic drugs not only to render patients unconscious, but also to induce a whole range of sedative states in a very precise and controlled fashion. Although no one

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can agree on whether loss of consciousness is resulting from a complex interplay of multiple neural causes or from a simple “switch-like” phenomenon, we as clinicians, know that we can induce, in any individual, a controlled change of consciousness along a wide range a behavioural states.

When applied to consciousness research, the simple clinical knowledge used daily by clinicians can provide exciting possibilities. The precise administration of anesthetic drugs is based on a solid scientific foundation that is well documented and relates to the fundamental concept of concentration-effect relationships.

Concentration-effect relationships

Anesthetic drugs are titrated to effect. The concentration or dosage needed to achieve a given behavioural change has been the subject of numerous studies and is very well known for many types of drugs, including inhalation anesthetics, benzodiazepines, propofol, barbiturates, opioids and ketamine. Research has not only been conducted during the administration of single drugs, but also using drug combinations to determine their synergistic effect.^{6,7} Moreover, the influence of covariates like weight,⁸ gender and age^{9,10} is now routinely determined and translated into standard recommendations for dosing.

While the net result is a better and safer context for the administration of anesthesia to patients, this knowledge, when applied to research on anesthetic drug action and consciousness, is fundamental and unique and constitutes the basis for our understanding of changes occurring in the CNS.

First, when applied to anesthesia research at the cellular level, it provides an upper limit concentration not to exceed. The concept of using “clinically relevant concentrations” is one that cannot be overlooked.

Second, when a drug is given to a patient or volunteer, the plasma concentration needed to achieve a given state of altered consciousness is known with precision. For effects ranging from the awake state to unconsciousness, validated sedation scales are used for objective evaluation.¹¹

But all this is not feasible without sophisticated tools for administration of drugs. For inhaled anesthetics, the availability of calibrated vaporizers and online gas analyzers allows for precise and immediate feedback on circulating concentrations. For *iv* drugs, online plasma concentration measurement is not yet possible, but the availability of computer controlled infusion pumps (CCIP) allows the researcher to obtain target plasma concentrations with surprising precision.^{12–14} CCIP use population pharmacokinetics to determine the infusion rate needed to immediately

reach and maintain a target plasma or effect site concentration. The scientific foundation for the use of this device is well established, and its precision has been validated in numerous publications.^{15,16}

In summary, the study of anesthetic drug effect on the CNS is based on the knowledge of concentration effect relationships and on the availability of tools that allows for obtaining stable plasma concentrations, and consequently and most importantly, stable effects.

In the following section, a few examples will be given to illustrate how research on mechanisms of anesthesia and on consciousness are interdependent.

Thalamo-cortical neurons

The critical role of thalamic nuclei in the maintenance of consciousness and the performance of cognitive functions is increasingly recognized. The transmission of afferent information to the cortex relies in great part on the integrity of thalamo-cortical neurons function. Ries and Puil have recently studied the effect of clinically relevant concentrations of isoflurane on thalamo-cortical neuron firing patterns. They reported that isoflurane hyperpolarized thalamo-cortical neurons and shunted voltage dependant sodium and calcium currents. They suggest that an enhanced potassium leak generalized in thalamo-cortical neurons alone could account for anesthesia *in vivo*.^{17,18}

In that study, the effect of isoflurane was assessed on neural cells that are instrumental in the maintenance of the conscious state. Thalamo-cortical neurons generate oscillatory patterns (40 Hz thalamo-cortical oscillations) that are thought to be mandatory for sustaining consciousness. These results point to the thalamic cellular events related to the loss of 40 Hz auditory steady-state and mid-latency auditory responses reported under anesthesia^{19,20} and support the hypothesis that loss of bursting firing patterns in the thalamo-cortical neurons and loss of consciousness are intimately linked.

Sleep, consciousness and anesthesia

Sleep and anesthesia share a number of physiological and behavioural traits.²¹ Obviously, they also differ in a significant number of ways, but the fact that they both result in a loss of consciousness suggests that they may share some common mechanistic features. Lydic *et al.* have been, for a number of years, interested in the effect of anesthetic drugs on acetylcholine (ACh) levels in the pontine reticular formation. Using microdialysis in living animals, they found that after the administration of morphine,²² halothane,²³ fentanyl²⁴ and ketamine,²⁵ the level of ACh decreased in the pontine reticular formation. Interestingly, pontine

ACh levels are also reduced during non REM sleep (for a review of this topic see Jones BE²⁶). The decrease in discharge of pontine cholinergic neurons projecting into the thalamus is also involved in electroencephalogram spindle generation^{27,28} (a feature common to sleep and halothane administration).

ACh has been shown to change as a function of the arousal state, leading to the hypothesis that the behavioural state induced by anesthesia might be, at least in part, related to changes in ACh levels. Interestingly, this view is supported by a number of anecdotal reports in which physostigmine, an acetylcholinesterase (AChE) inhibitor that crosses the blood-brain barrier, decreased the time to awaken from anesthesia, and modulated or simply reversed the effect of anesthetic drugs on consciousness. In a series of studies done on volunteers, our group showed that unconsciousness caused by propofol,²⁹ remifentanyl,³⁰ and to a lesser extent, sevoflurane, was reversed by physostigmine, and that the reversal was blocked by the pre-administration of scopolamine, a muscarinic antagonist. These results suggest that the muscarinic system, which plays an important role in the maintenance of the conscious state³¹ is affected by the administration of anesthetic drugs. They also stress the fact that anesthesia is not only affecting a single neurotransmitter system like GABA or NMDA, but rather induces a series of direct or indirect effects on multiple systems related to consciousness.

Using anesthetic drugs as modulators

Whether the loss of a given cognitive function, like memory for example, during the administration of a drug occurs in a stepwise or a graded fashion is still a matter of conceptual and methodological debate. Likewise, it is not yet possible to determine how and if consciousness is lost at a precise moment in time, and if this happens as a result of a discrete neurophysiological event or as the endpoint of a conjunction of factors. Knowledge of concentration-effect relationships of anesthetic drugs provides an opportunity to induce reversible alterations in cognitive functions and study their neural correlates.

This approach has been used by Veselis *et al.*,³² in their studies on memory during anesthesia. Based on the premisses that the effect of certain anesthetic drugs on memory seem to be specific and separate from their sedative hypnotic effects, they gave propofol to two groups to induce two levels of memory impairment based on word recognition. They measured regional cerebral blood flow with positron emission tomography with the hypothesis that drug effects are likely mediated in the neuroanatomical regions or

networks that subserve these effects. They found that reductions in rCBF occurred in brain regions identified with working memory processes but that, in contrast, medial temporal lobe structures (i.e., hippocampus) were resistant. They concluded that: "the memory effect of propofol is produced by interference with distributed cortical processes necessary for normal memory function rather than specific effects on medial temporal lobe structures".³² These results may shed light not only on propofol drug effect, but also on the complex integrated interplay between working memory and encoding.

Our group has studied the effect of propofol targeting plasma concentrations typically needed to induce light, deep sedation and unconsciousness using brain imaging not only to determine the primary effects of the anesthetic itself³³ but also to determine its influence on cortical activation evoked by vibro-tactile stimulation,³⁴ pain³⁵ or sound. The CNS areas primarily affected by propofol were those typically involved in the maintenance of the conscious state, but also those that are active at the resting state. Gusnard and Raichle³⁶ compared our results with those from other studies in which consciousness had been lost during sleep or coma. Some areas common to all forms of altered consciousness were deactivated, like the posterior cingulate and the cuneus and pre-cuneus. They hypothesized that these areas are part of a network that is responsible for the existence of a baseline resting state of the brain, a state that allows us to be awake, and ready to process incoming information. This concept, also referred to as the "default mode of brain function"^{37,38} is the subject of a growing interest in neuroscience related to consciousness.³⁹ This last example illustrates how research on mechanisms of anesthesia serves the double purpose of advancement in our knowledge of drug action and determination of mechanisms involved in conscious states.

Conclusion

It is fundamental for our specialty to elucidate the mechanisms by which anesthetic drugs exert their action. It now seems that anesthesia is not the result of a generalized and non-specific action of drugs on the CNS, but occurs due to a complex action on cell membranes, specific ion channels and discrete parts of the CNS. The fact that we can induce discrete and dose-specific effects on attention, pain appreciation, memory, complex cognitive functions or consciousness itself suggests that our drugs act on specific parts of the CNS. From a broader perspective, it also means that we can use our clinical expertise to induce controlled modulation of cognitive functions in order to uncover their neural correlates. In the end, research

on anesthetic mechanisms and consciousness are not dissociable because understanding our tools also helps to define the substrate.

References

- 1 Zeman A. Consciousness. *Brain* 2001; 124: 1263–89.
- 2 Von Economo C. Encephalitis Lethargica: its Sequelae and Treatment. London: Oxford University Press; 1931.
- 3 Bremer F. Cerveau "isolé" et physiologie du sommeil. *C R Seanc Soc Biol* 1929; 102: 1235–41.
- 4 Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. *Electroencephalogr Clin Neurophysiol* 1949; 1: 455–73.
- 5 Steriade M, Jones EG, Llinás RR. Brainstem control of the thalamus and states of vigilance, Thalamic oscillations and signaling. In: Steriade M, Jones EG, Llinás RR (Eds). *There is a Remarkable Consistency in the Location of Such Changes in the Thalamus Across the Variety of Sleep-Waking States*. New York: John Wiley & Sons; 1990: 313–64.
- 6 Vuyk J, Mertens MJ, Olofsen E, Burm AGL, Bovill JG. Propofol anesthesia and rational opioid selection. *Anesthesiology* 1997; 87: 1549–62.
- 7 Kazama T, Ikeda K, Morita K. The pharmacodynamic interaction between propofol and fentanyl with respect to the suppression of somatic or hemodynamic responses to skin incision, peritoneum incision, and abdominal wall retraction. *Anesthesiology* 1998; 89: 894–906.
- 8 Egan TD, Huizinga B, Gupta S, et al. Remifentanyl pharmacokinetics in obese versus lean patients. *Anesthesiology* 1998; 89: 562–73.
- 9 Minto CF, Schnider TW, Egan TD, et al. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl I. Model development. *Anesthesiology* 1997; 86: 10–23.
- 10 Dyck JB, Shafer SL. Effects of age on propofol pharmacokinetics. *Seminars in Anesthesia* 1992; 11: 2–4.
- 11 Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10: 244–51.
- 12 Vuyk J, Engbers FHM, Burm AGL, Vletter AA, Bovill JG. Performance of computer-controlled infusion of propofol: an evaluation of five pharmacokinetic parameter sets. *Anesth Analg* 1995; 81: 1275–82.
- 13 Gustaffson LL, Ebling WF, Osaki E, Harapat S, Stanski DR, Shafer SL. Plasma concentration clamping in the rat using a computer-controlled infusion pump. *Pharma Res* 1992; 9: 800–7.
- 14 Swinhoe CF, Peacock JE, Glen JB, Reilly CS. Evaluation of the predictive performance of a "Diprifusor" TCI system. *Anaesthesia* 1998; 53: 61–7.
- 15 Shafer SL, Gregg K. Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. *J Pharmacokinet Biopharm* 1992; 20: 147–69.
- 16 Varvel JR, Donoho DL, Shafer SL. Measuring the predictive performance of computer controlled infusions. *J Pharmacokinet Biopharm* 1992; 20: 63–94.
- 17 Ries CR, Puil E. Mechanism of anesthesia revealed by shunting actions of isoflurane on thalamocortical neurons. *J Neurophysiol* 1999; 81: 1795–801.
- 18 Ries CR, Puil E. Ionic mechanism of isoflurane's actions on thalamocortical neurons. *J Neurophysiol* 1999; 81: 1802–9.
- 19 Meuret P, Backman SB, Bonhomme V, Plourde G, Fiset P. Physostigmine reverses propofol-induced unconsciousness and attenuation of the auditory steady state response and bispectral index in human volunteers. *Anesthesiology* 2000; 93: 708–17.
- 20 Plourde G, Villemure C, Fiset P, Bonhomme V, Backman SB. Effects of isoflurane on auditory steady state response and on unconsciousness in human volunteers. *Anesthesiology* 1998; 89: 844–51.
- 21 Lydic R, Biebuyck JF. Sleep neurobiology: relevance for mechanistic studies of anaesthesia. *Br J Anaesth* 1994; 72: 506–8.
- 22 Lydic R, Keifer JC, Baghdoyan HA, Becker BS. Microdialysis of the pontine reticular formation reveals inhibition of acetylcholine release by morphine. *Anesthesiology* 1993; 79: 1003–12.
- 23 Keifer JC, Baghdoyan HA, Lydic R. Pontine cholinergic mechanisms modulate the cortical electroencephalographic spindles of halothane anaesthesia. *Anesthesiology* 1996; 84: 945–54.
- 24 Mortazavi S, Thompson J, Baghdoyan HA, Lydic R. Fentanyl and morphine, but not remifentanyl, inhibit acetylcholine release in pontine regions modulating arousal. *Anesthesiology* 1999; 90: 1070–7.
- 25 Lydic R, Baghdoyan HA, Becker L, Beibuyck JF. Systemic ketamine causes dose-dependent alterations in acetylcholine (ACh) release within the medialpontine reticular formation (mPRF). *Soc Neurosci* 1994; 20: 40.7.
- 26 Jones BE. Basic Mechanisms of Sleep-Wake States, Principles and Practice of Sleep Medicine, 2nd Ed. In: Kryger MH, Roth T, Dement WC (Eds.). Philadelphia: W.B. Saunders; 1994: 145–62.
- 27 Steriade M, Dossi RC, Pare D, Oakson G. Fast oscillations (20–40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proc Natl Acad Sci USA* 1991; 88: 4396–400.
- 28 Pare D, Smith Y, Parent A, Steriade M. Projections of brainstem core cholinergic and non-cholinergic neurons of cat to intralaminar and reticular thalamic

- nuclei. *Neuroscience* 1988; 25: 69–86.
- 29 *Bonhomme V, Plourde G, Meuret P, Fiset P, Backman SB.* Auditory steady-state response and bispectral index for assessing level of consciousness during propofol sedation and hypnosis. *Anesth Analg* 2000; 91: 1398–403.
 - 30 *Talbot M, Plourde G, Backman SB, Chartrand D, Fiset P.* Effect of physostigmine on the loss of consciousness and analgesia produced by remifentanyl. *Anesthesiology* 2000; 93: 389 (abstract).
 - 31 *Durieux ME.* Muscarinic signaling in the central nervous system. Recent developments and anesthetic implications. *Anesthesiology* 1996; 84: 173–89.
 - 32 *Veselis RA, Reinsel RA, Feshchenko VA, Dnistrian AM.* A neuroanatomical construct for the amnestic effects of propofol. *Anesthesiology* 2002; 97: 329–37.
 - 33 *Fiset P, Paus T, Daloze T, et al.* Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomography study. *J Neurosci* 1999; 19: 5506–13.
 - 34 *Bonhomme V, Fiset P, Meuret P, et al.* Effect of propofol-induced general anesthesia on changes in regional cerebral blood flow elicited by vibrotactile stimulation: a positron emission tomography study. *J Neurophysiol* 2001; 85: 1299–308.
 - 35 *Hofbauer RK, Daloze T, Fiset P, Plourde G, Backman SB, Bushnell MC.* Effect of propofol-induced sedation and loss of consciousness on pain-related activity in the human forebrain. *Soc Neurosci* 1999; 25: 59.6.
 - 36 *Gusnard DA, Raichle ME.* Searching for a baseline: functional imaging and the resting human brain. *Nature Rev Neurosci* 2001; 2: 685–94.
 - 37 *Binder JR, Frost JA, Hammeke TA, Bellgowan PSF, Rao SM, Cox RW.* Conceptual processing during the conscious resting state: a functional MRI study. *J Cognit Neurosci* 1999; 11: 80–93.
 - 38 *Mazoyer B, Zago L, Mellet E, et al.* Cortical networks for working memory and executive functions sustain the conscious resting state in man. *Brain Res Bull* 2001; 54: 287–98.
 - 39 *Greicius MD, Krasnow B, Reiss AL, Menon V.* Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proc Natl Acad Sci* 2003; 100: 253–8.