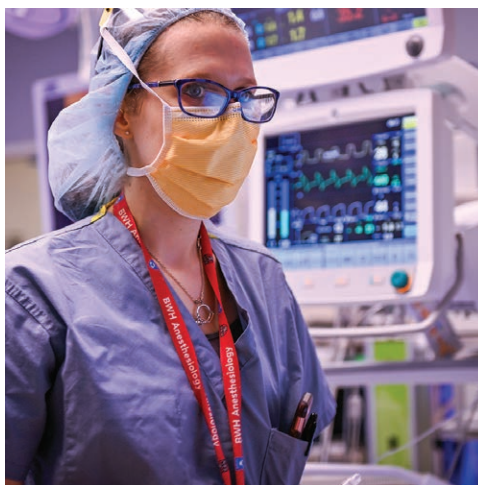


Anesthesia Mechanisms: A Patchwork Quilt rather than a Wet Blanket?

Logan Voss, Ph.D., Jamie W. Sleight, M.D.

Scientific models attempt to be the best representations of the available facts. The so-called “wet blanket” model of anesthetic action assumed that anesthetic drugs distribute evenly to all brain regions and nonspecifically dampen down the fire of global neuronal activity, leading to the unresponsive anesthetized state. Over time it has become clear that specific brain regions contribute to different behavioral anesthetic effects, such as amnesia (hippocampus) and immobility (spinal cord). Technological advances that enable ever greater spatial and physiologic resolution continue to refine our understanding of where and how anesthetics work in the brain.

In this issue of *ANESTHESIOLOGY*, Melonakos *et al.* report on anesthetic interactions within the dorsal pontine region of the ascending reticular activating system, known as the parabrachial nucleus.¹ Utilizing a cutting-edge technique known as Designer Receptors Exclusively Activated by Designer Drugs (DREADDs), the authors investigated whether parabrachial nucleus excitation could reverse dexmedetomidine or ketamine sedation. DREADDs methodology is a complex mix of viral vector and inducible gene technology, allowing individual nuclei or groups of neurons to be manipulated with exquisite specificity.² In this case, glutamatergic neurons in the parabrachial nucleus were switched on or off at will, and the effect on the wider brain network was observed. This paper is a quintessential example, showcasing the sophisticated tools now available to explore the function of highly localized subregions of the brain. The authors found that parabrachial excitation had minimal effects on electroencephalogram delta waves or on the recovery time for high-dose dexmedetomidine or low-dose ketamine, but paradoxically *prolonged* the recovery time



“Are we closer to actively waking a patient from general anesthesia, rather than just waiting for passive elimination of hypnotic drugs?”

from high-dose ketamine. These findings contrast with previous work with DREADD activation of the parabrachial nucleus that demonstrated dramatically accelerated emergence from anesthesia, which included a γ -aminobutyric acid-mediated (GABAergic) component of drug action (propofol and volatile anesthetics).^{3,4} How can we make sense of these observations in a wider context, and what is their clinical relevance?

The ascending reticular activating system was originally described as a diffuse brain stem arousal system necessary for wakeful behavior, based on its widespread excitatory projections to the thalamus and cerebral cortex and the decreased arousal caused by lesions of this system. However, over the last two decades, there has been a steady stream of investigations helping to dissect out the role specific arousal nuclei play within this system and how anesthetics interact with these targets. For example, studies have shown that unresponsiveness can be induced by microinjection of anesthetic drugs in specific regions,⁵ or conversely, that animals could be awakened from light anesthesia by activating various nuclei using neuromodulators and electrical stimulation.^{6,7} This has given rise to the notion that general anesthetic agents—to some extent, at least—harness and exaggerate localized brainstem components of natural GABAergic sleep mechanisms. The wet blanket is starting to resemble a patchwork quilt.

There is a body of evidence that the glutamatergic neurons in the medial parabrachial nucleus play a central role in controlling wakefulness—as these neurons project to, and coactivate, many other wake-promoting regions (the basal forebrain, intralaminar thalamus, lateral hypothalamus, ventral tegmental area, and locus ceruleus). Parabrachial DREADDs-stimulated glutamatergic activity is sufficient

Image: J. P. Rathmell.

This editorial accompanies the article on p. 633.

Accepted for publication June 11, 2021. From the Department of Anaesthesiology, Waikato Clinical Campus, Faculty of Medical and Health Sciences, University of Auckland, Hamilton, New Zealand.

Copyright © 2021, the American Society of Anesthesiologists. All Rights Reserved. *Anesthesiology* 2021; 135:568–9. DOI: 10.1097/ALN.0000000000003879

to reanimate animals, in the presence of less than about 0.8 minimum alveolar concentration (MAC) equivalent of GABAergic hypnotic drugs.³ Thus, when the brain is already quite close to the tipping point between sleep and wakefulness, full reversal can be achieved when natural sleep mechanisms are antagonized. With higher concentrations of GABAergic hypnotic drugs, other direct cortical suppressant effects are sufficiently strong to oppose the subcortical activation, and so prevent emergence.

Why are these effects not replicated with dexmedetomidine and ketamine? The authors discuss some possibilities, but clearly their results indicate the presence of other arousal systems that lie in series with that of the parabrachial nucleus. These collateral actions dominate at higher dexmedetomidine concentrations. This would explain the unique flavor and features of dexmedetomidine sedation and also why it potentiates GABAergic sedative drugs. Further, why does ketamine appear to *require* extra glutamate for its hypnotic effect? This strange observation agrees with other work showing that intact mitochondrial reserve is a prerequisite for ketamine hypnotic effects,⁸ and that ketamine increases frontal lobe glutamate recycling.⁹ The implication is that ketamine *causes hypnosis* by an energy-dependent process supporting active glutamatergic signaling.

To what extent can we extrapolate these animal studies to clinical anesthesia? Are we closer to actively waking a patient from general anesthesia, rather than just waiting for passive elimination of hypnotic drugs? Safety and ethical constraints clearly preclude the clinical use of DREADD technology. However, the information generated from this technology may point us to specific subtypes of receptors that would be amenable to future targeted drug therapy. It is also worth noting that many of the drugs currently used as adjuncts in anesthesia (for example, anticholinergic, antiemetic, and antihistaminergic agents) act on nuclei in the ascending reticular activating system to impede emergence from anesthesia.

With ever increasing functional localization, perhaps there's a risk of losing sight of the proverbial forest for the trees. While the wet blanket view of anesthetic action is much too simplistic, it is nevertheless helpful to view this patchwork of mechanistic studies through a "wet blanket" lens. Anesthetics affect the brain globally but not uniformly. At the risk of overextending the metaphor, some parts of the patchwork blanket are made of toweling and absorb a lot of water, and some are made of leather and are only dampened at high concentrations—but still prevent the fire from igniting. Furthermore, the patchwork is interconnected, functionally interdependent, and highly wickable. Ultimately, it is the cumulation and integration of specific actions at multiple locations that characterizes general anesthesia. *Pro tempore*, anesthesia resembles a damp patchwork.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Sleight: jamie.sleight@waikato.dhb.health.nz

References

1. Melonakos ED, Siegmann MJ, Rey C, O'Brien C, Nikolaeva KK, Solt K, Nehs CJ: Excitation of putative glutamatergic neurons in the rat parabrachial nucleus region reduces delta power during dexmedetomidine but not ketamine anesthesia. *ANESTHESIOLOGY* 2021; 135:633–48
2. Melonakos ED, Moody OA, Nikolaeva K, Kato R, Nehs CJ, Solt K: Manipulating neural circuits in anesthesia research. *ANESTHESIOLOGY* 2020; 133:19–30
3. Wang TX, Xiong B, Xu W, Wei HH, Qu WM, Hong ZY, Huang ZL: Activation of parabrachial nucleus glutamatergic neurons accelerates reanimation from sevoflurane anesthesia in mice. *ANESTHESIOLOGY* 2019; 130:106–18
4. Luo T, Yu S, Cai S, Zhang Y, Jiao Y, Yu T, Yu W: Parabrachial neurons promote behavior and electroencephalographic arousal from general anesthesia. *Front Mol Neurosci* 2018; 11:420
5. Avigdor T, Minert A, Baron M, Devor M: Paradoxical anesthesia: Sleep-like EEG during anesthesia induced by mesopontine microinjection of GABAergic agents. *Exp Neurol* 2021; 343:113760
6. Muindi F, Kenny JD, Taylor NE, Solt K, Wilson MA, Brown EN, Van Dort CJ: Electrical stimulation of the parabrachial nucleus induces reanimation from isoflurane general anesthesia. *Behav Brain Res* 2016; 306:20–5
7. Taylor NE, Chemali JJ, Brown EN, Solt K: Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. *ANESTHESIOLOGY* 2013; 118:30–9
8. Quintana A, Morgan PG, Kruse SE, Palmiter RD, Sedensky MM: Altered anesthetic sensitivity of mice lacking Ndufs4, a subunit of mitochondrial complex I. *PLoS One* 2012; 7:e42904
9. Abdallah CG, De Feyter HM, Averill LA, Jiang L, Averill CL, Chowdhury GMI, Purohit P, de Graaf RA, Esterlis I, Juchem C, Pittman BP, Krystal JH, Rothman DL, Sanacora G, Mason GF: The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects. *Neuropsychopharmacology* 2018; 43:2154–60