Commentary

Dopamine in the ventral tegmental area facilitates emergence from general anesthesia

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Taylor *et al*. (1) showed that optogenetic activation of dopaminergic neurons in the ventral tegmental area (VTA) during continuous, steady-state isoflurane-induced general anesthesia produced electrographic arousal, and restored the righting reflex in mice. Systemic administration of the D1 receptor antagonist SCH-23390 before optical stimulation greatly attenuated electrographic and behavioral arousal. Transfection of VTA neurons with a vector carrying channelrhodopsin 2 (ChR2) allowed optical activation, and optical stimulation in control mice transfected with a vector lacking ChR2 did not induce arousal.

This study used state-of-the-art techniques to selectively activate dopaminergic neurons. It was among the first to use optogenetic techniques in the study of the neural mechanism of general anesthesia. Immunocytochemistry indicated that about 40% of the VTA neurons were transfected with ChR2, and histological verification of the optical fiber above VTA was given. Direct demonstration of dopaminergic neuron firing was not provided. However, 30–50 Hz stimulation with light pulses of 5–10 ms duration closely resembled the 25-Hz stimulation protocol shown to be optimal in activating ChR2-transfected dopaminergic neurons (2).

Optogenetic stimulation of the VTA dopaminergic neurons activated the electroencephalogram recorded epidurally in mice, shown as a decrease in the spectral power of slow waves of <2 and 6–17 Hz. Most intriguingly, optogenetic stimulation of the VTA dopaminergic neurons restored the righting reflex during continuous 0.8% isoflurane administration. The effective dose (ED50) for a loss of righting reflex in mice was not given, but this was likely around 0.8% (3). The authors showed that their control mice did not recover righting despite optical stimulation of the VTA during continuous 0.8% isoflurane. A continuous isoflurane protocol is a method to show emergence under a controlled anesthetic dose. In real life, emergence is accompanied by a rapid decrease of gaseous anesthetic in the lungs and brain, while drugs like methylphenidate could be used to hasten emergence (4).

This study provides insights to the divide between behavior and general anesthesia. VTA dopaminergic neuronal firing activity did not correlate with sleep-wake activity in cats, but was higher generally during active waking than quiet waking (5). Neurons firing during active waking may provide a neural substrate to resist general anesthesia (6), and VTA dopaminergic neurons are an example.

The study supports the notion that the limbic system influences general anesthesia (6-8). Within the limbic system, the nucleus accumbens is proposed to translate motivation to action, facilitated by the VTA mesolimbic dopaminergic system (9,10). Arousal from general anesthesia appears to be in line with combined motivation-motor functions of VTA dopamine, without which there will be a "decreased willingness to exert effort" (11).

Electrical stimulation of the VTA, but not the substantia nigra, promoted emergence from isoflurane anesthesia (12). Dopaminergic neurons in the substantia nigra, which project to the caudate/putamen, are apparently more concerned with execution of movements (13,14) than motivating action.

The recovery of righting reflex in animals is associated with regaining of consciousness in humans, shown as responding to verbal commands. Thus, emergence from general anesthesia in humans may be facilitated by a "will power" provided by the VTA dopaminergic system, which prevents the lapse into unconsciousness. The VTA system will likely animate discussion of the neural substrates of consciousness among neuroscientists and philosophers. Connections between neocortical areas, suggested to be the basis of consciousness (15), are likely not directly modulated by VTA dopaminergic stimulation.

Other than inducing arousal, VTA dopaminergic neurons may also facilitate cognitive functions of the prefrontal and hippocampal cortices, some of which are mediated by D1 receptors. On the other hand, dopamine in the mesolimbic system is also associated with hyperlocomotion (animal model of delirium) during anesthesia induction or emergence in rodents (7,16). Whether early emergence from general anesthesia is beneficial for patients may depend on whether it can be managed without dyscognitive and delirious effects.

Selective lesion of dopaminergic neurons in the VTA was shown to prolong emergence from propofol but not isoflurane anesthesia (17). Stimulation of VTA dopaminergic neurons likely works by recruiting neural circuits that involve limbic cortices, nucleus accumbens, and pedunculopontine nucleus (6,9,18). The role of other wake-active neurons in the emergence from general anesthesia (6,19) remains to be clarified, including neurons using neurotransmitter acetylcholine, histamine, norepinephrine (20), serotonin and orexin. In conclusion, other than finding that optogenetic activation of the VTA dopaminergic neurons was sufficient to arouse the brain from isoflurane anesthesia, Taylor *et al*. (1) have unveiled a research vista of how the brain and general anesthesia compete for the control of behavior.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Taylor NE, Van Dort CJ, Kenny JD, et al. Optogenetic activation of dopamine neurons in the ventral tegmental area induces reanimation from general anesthesia. Proc Natl Acad Sci U S A 2016. [Epub ahead of print].
2. Adamantidis AR, Tsai HC, Boutrel B, et al. Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. J Neurosci 2011;31:10829-35.
3. Kelz MB, Sun Y, Chen J, et al. An essential role for orexins in emergence from general anesthesia. Proc Natl Acad Sci U S A 2008;105:1309-14.
4. Solt K, Cotten JF, Cimenser A, et al. Methylphenidate actively induces emergence from general anesthesia. Anesthesiology 2011;115:791-803.
5. Trulson ME, Preussler DW. Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep-waking cycle and effects of stress. Exp Neurol 1984;83:367-77.
6. Leung LS, Luo T, Ma J, et al. Brain areas that influence general anesthesia. Prog Neurobiol 2014;122:24-44.
7. Ma J, Leung LS. Limbic system participates in mediating the effects of general anesthetics. Neuropsychopharmacology 2006;31:1177-92.
8. Ma J, Shen B, Stewart LS, et al. The septohippocampal system participates in general anesthesia. J Neurosci 2002;22:RC200.
9. Mogenson GJ, Brudzynski SM, Wu M, et al. From motivation to action: a review of dopaminergic regulation of limbic- nucleus accumbens-pedunculopontine nucleus circuitries involved in limbic-motor integration. In: Kalivas PW, Barnes CD. editors. Limbic Motor Circuits and Neuropsychiatry. Boca Raton: CRC Press, 1993:193-236.
10. Wise RA. Dopamine, learning and motivation. Nat Rev Neurosci 2004;5:483-94.
11. Neill DB, Justice JB. An hypothesis for a behavioral function of dopaminergic transmission in nucleus accumbens. In: Chronister RB, DeFrance JF. editors. The Neurobiology of the Nucleus Accumbens. New Brunswick: Haer Institute, 1981:343-50.
12. Solt K, Van Dort CJ, Chemali JJ, et al. Electrical

stimulation of the ventral tegmental area induces reanimation from general anesthesia. Anesthesiology 2014;121:311-9.
13. Pioli EY, Meissner W, Sohr R, et al. Differential behavioral effects of partial bilateral lesions of ventral tegmental area or substantia nigra pars compacta in rats. Neuroscience 2008;153:1213-24.
14. Boekhoudt L, Omrani A, Luijendijk MC, et al. Chemogenetic activation of dopamine neurons in the ventral tegmental area, but not substantia nigra, induces hyperactivity in rats. Eur Neuropsychopharmacol 2016;26:1784-93.
15. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. Science 2008;322:876-80.
16. Irifune M, Sato T, Nishikawa T, et al. Hyperlocomotion during recovery from isoflurane anesthesia is associated with increased dopamine turnover in the nucleus accumbens and striatum in mice. Anesthesiology 1997;86:464-75.
17. Zhou X, Wang Y, Zhang C, et al. The Role of Dopaminergic VTA Neurons in General Anesthesia. PLoS One 2015;10:e0138187.
18. Martinez-Gonzalez C, Bolam JP, Mena-Segovia J. Topographical organization of the pedunculopontine nucleus. Front Neuroanat 2011;5:22.
19. Saper CB, Fuller PM, Pedersen NP, et al. Sleep state switching. Neuron 2010;68:1023-42.
20. Vazey EM, Aston-Jones G. Designer receptor manipulations reveal a role of the locus coeruleus noradrenergic system in isoflurane general anesthesia. Proc Natl Acad Sci U S A 2014;111:3859-64.

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