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

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