Dopamine-enhancing Medications to Accelerate Emergence from General Anesthesia

DOPAMINERGIC neurotransmission is prominently implicated in emergence from the minimal conscious state,[1,2] general anesthesia,[3] and in sleep–wake regulation.[4] The molecular mechanisms for these effects are still incompletely understood. The anatomical and neurochemical signatures of the dopamine (DA) system for arousal under conditions of general anesthesia are clinically important to understand. First, from a clinical point of view, accurate knowledge of the molecular basis for emergence from general anesthetics with agents for which no specific antagonists exists (*i.e.*, inhalational agents) and for other anesthetic regimens could lead to the development of a range of new drugs specifically designed for rapid emergence. Such therapeutics could perhaps be useful in the future for routine anesthesia practice. For example, rapid arousal of elderly patients undergoing surgical procedures requiring general anesthesia may prove valuable for reducing cognitive dysfunction and/or early delirium postoperatively. Second, a better understanding of the neuronal mechanisms by which DA increases the emergence from anesthesia will also help in the management of patients with DA abnormalities as may be the case for patients with Parkinson disease, schizophrenic patients treated with depot neuroleptics (long-acting dopamine-2 receptor [D2R] antagonists) and drug abusers.

"The anatomical and neurochemical signatures of the dopamine system for arousal under conditions of general anesthesia are clinically important to understand."

In this issue of Anesthesiology, Taylor *et al.*[5] report that the dopamine-1 receptor (D1R) agonist 6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide but not the D2R agonist quinpirole reduces the time to emergence from isoflurane anesthesia in rats by 85% compared with placebo. The authors conclude that selective activation of D1Rs is sufficient to induce emergence from isoflurane general anesthesia and that D2Rs are not needed.[5] These new data in the setting of isoflurane anesthesia are intriguing and supplement older data reporting similar findings with phenobarbital anesthesia.[6,7] Specifically, Horita *et al.*[7] investigated the effects of a D1R agonist (1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol) and a D2R antagonist (raclopride) on duration of phenobarbital anesthesia in rats (administered only 20 min after induction with 40 mg/kg intraperitoneal phenobarbital to reduce pharmacokinetic effects on emergence). They documented that the D1R agonist reduced the time to emergence by approximately 30% and found that this effect could be abolished by a D1R antagonist.[7] However, in contrast to the current study,[5] Horita *et al.*[7] reported that the D2R antagonist raclopride and atropine also reversed the effect of the D1R agonist. Thus, the findings of Horita *et al.* suggest that the arousing effects of D1R agonists require the coactivation of these two receptors (D1R and D2R). Interestingly, although nonsignificant, the study by Taylor *et al.*[5]showed decreases in the time from emergence of anesthesia in the rats treated with the D2R agonist quinpirole (from 330 to 189 s) and had their sample (n = 6) been larger, this effect may have been significant. Regardless, it is clear that the effects of the D1R agonist was stronger than that of the D2R agonist (quinpirole), which could reflect in part its effects on D2R autoreceptors that would lead to a decrease in DA release. In the previous study, Horita *et al.*[7] also provide evidence that the dopaminergic effects (driven by D1R but presumably requiring background D2R tone) are mediated by downstream cholinergic effects (because these effects were blocked by atropine). In the context of the importance of D2Rs, Solt *et al.*[3] reported that

Photo: ©Thinkstock.

Accepted for publication August 28, 2012. 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. Dr. Volkow's research was supported by the National Institutes of Health's Intramural Research Program (NIAAA).

◆ This Editorial View accompanies the following article: Taylor NE, Chemali JJ, Brown EN, Solt K: Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology 2013; 118:30–9.

droperidol (a potent D2 antagonist) abolished the ability of the DA-enhancing drug methylphenidate to accelerate emergence in rats anesthetized with isoflurane, which also strongly suggests that D2Rs are important for anesthesia emergence.

Another intriguing question is which brain pathways mediate the effects of DA in emergence from anesthesia. In general, studies on DA networks have focused mostly on pathways involved with movement (mesostriatal), reward (mesoaccumbens), and cognition (mesocortical), and much less is known about the DA pathways implicated in arousal. Although it is plausible that some or all of these DA pathways participate in arousal, it is also likely that DA mediates its arousing effects through additional brain-wide systems. For example, the orexin/hypocretin lateral hypothalamic nucleus, which mediates arousal and is implicated in narcolepsy, is modulated by both D1R and D2R.[8,9] Similarly, the tuberomammillary nucleus, which is involved in the control of wakefulness, signals not only through histamine receptors but also through D1R and D2R.[10] In addition, as discussed by Taylor *et al.*,[5] DA neurons in the ventral periaqueductal gray could mediate the effects of DA on the emergence from anesthesia.[11] Finally, it is also possible that DA mediates its effects on arousal *via* thalamic activation.[12]

Over the past decades, scientists have studied the DA system's role in cognition, motor behavior, and reward and its disruption in neuropsychiatric diseases. The data of Taylor *et al.*[5] and that of others now highlight the importance of DA in arousal. These findings have direct clinical implications for the practice of anesthesia for they may help direct the development of new medications to accelerate the emergence from anesthesia.

Helene Benveniste, M.D., Ph.D.,* Nora D. Volkow, M.D.† *Department of Anesthesiology, Health Sciences Center, Stony Brook University, Stony Brook, New York. helene.benveniste@sbumed.org. †National Institute of Drug Abuse, Bethesda, Maryland.

References

1. Zafonte RD, Lexell J, Cullen N: Possible applications for dopaminergic agents following traumatic brain injury: Part 2. J Head Trauma Rehabil 2001; 16:112–6
2. Zafonte RD, Lexell J, Cullen N: Possible applications for dopaminergic agents following traumatic brain injury: Part 1. J Head Trauma Rehabil 2000; 15:1179–82
3. Solt K, Cotten JF, Cimenser A, Wong KF, Chemali JJ, Brown EN: Methylphenidate actively induces emergence from general anesthesia. Anesthesiology 2011; 115:791–803
4. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM: Dopaminergic role in stimulant-induced wakefulness. J Neurosci 2001; 21:1787–94
5. Taylor NE, Chemali JJ, Brown EN, Solt K: Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology 2013; 118:30–9
6. Horita A, Carino MA: D-1 agonist, SKF 38393, but not a D-2 agonist, produces a cholinergically mediated analeptic effect in rabbits. Pharmacol Biochem Behav 1991; 39:449–52
7. Horita A, Carino MA, Nishimura Y: D1 agonist SKF 38393 antagonizes pentobarbital-induced narcosis and depression of hippocampal and cortical cholinergic activity in rats. Life Sci 1991; 49:595–601
8. Rao Y, Liu ZW, Borok E, Rabenstein RL, Shanabrough M, Lu M, Picciotto MR, Horvath TL, Gao XB: Prolonged wakefulness induces experience-dependent synaptic plasticity in mouse hypocretin/orexin neurons. J Clin Invest 2007; 117:4022–33
9. Bubser M, Fadel JR, Jackson LL, Meador-Woodruff JH, Jing D, Deutch AY: Dopaminergic regulation of orexin neurons. Eur J Neurosci 2005; 21:2993–3001
10. Yanovsky Y, Li S, Klyuch BP, Yao Q, Blandina P, Passani MB, Lin JS, Haas HL, Sergeeva OA: L-Dopa activates histaminergic neurons. J Physiol (Lond) 2011; 589(Pt 6):1349–66
11. Lu J, Jhou TC, Saper CB: Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. J Neurosci 2006; 26:193–202
12. Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Wong C, Ma J, Pradhan K, Tomasi D, Thanos PK, Ferré S, Jayne M: Sleep deprivation decreases binding of [11C]raclopride to dopamine D2/D3 receptors in the human brain. J Neurosci 2008; 28:8454–61.