

From the Edge of Oblivion

The Dance between Intrinsic Neuronal Currents and Neuronal Connectivity

WHAT are the neurobiological processes required for patients to wake up after anesthesia? Historically, emergence from anesthesia has been considered to be a passive process dependent only upon redistribution or elimination of the anesthetic drugs from their central effect sites. It is increasingly evident that this is not correct. The process of waking up from general anesthesia is not just the inverse of induction.¹ In this issue of ANESTHESIOLOGY there is a paper by Chemali *et al.* reporting on the efficacy of methylphenidate in actively awakening rats from propofol hypnosis.² In summary, their results showed that administration of a substantial dose (5 mg/kg) of intravenous methylphenidate almost halved the period of loss-of-righting reflex induced by a bolus dose (8 mg/kg) of intravenous propofol. Methylphenidate also caused both electroencephalographic and behavioral arousal in animals during maintenance of a target-controlled propofol infusion, which had been titrated to be just sufficient to achieve unresponsiveness. These activating effects are attributed to the known action of methylphenidate in increasing cortical dopamine, with the possible contribution of norepinephrine signaling as well. The results from this study add to previous work done by this group, in which they demonstrated similar methylphenidate-induced reversal of isoflurane hypnosis. Moreover, methylphenidate's effects are broadly comparable with previous reports of systemic delivery of physostigmine to patients receiving a



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fatigued patients, and also in those patients receiving drugs (such as antihistamines, anticholinergics, and clonidine) that impair the brainstem arousal mechanisms. Arousal-promoting neuromodulators act primarily to alter the membrane potential and intrinsic excitability of the neurons, mainly by activation of intracellular calcium and cyclic adenosine monophosphate, and closure of potassium channels.⁹ Although variation in intrinsic currents can secondarily influence synaptic efficiency, the neuromodulators tend not to have direct effects on synaptic strength. The fact that several distinct neuromodulators can reverse hypnosis would suggest that there is substantial redundancy in the arousal systems, but also that the arousal systems

target-controlled infusion of propofol³; and microinjections of nicotinic agonists,⁴ potassium channel blockers,⁵ norepinephrine,⁶ histamine,⁷ and orexin⁸ targeted to specific subcortical regions. These studies give us some valuable insight into the delicate dance between general anesthetic drugs and the natural wake and sleep systems of the brain.

At the risk of some oversimplification, we can make two conclusions. First, in the presence of low or medium (0.5–0.7 minimum alveolar concentration) concentrations of volatile anesthetic agent—or the equivalent amount of propofol—administration of a compound which augments or simulates the action of natural arousal-promoting, neuromodulator substances (such as amines, acetylcholine, orexin, or glutamate) will accelerate anesthetic emergence. By activating a number of natural wake-promoting brain systems, we appear to be able to induce a partial physiologic antagonism to general anesthesia. The results are consistent with clinical reports of delayed emergence from general anesthesia in narcoleptic and

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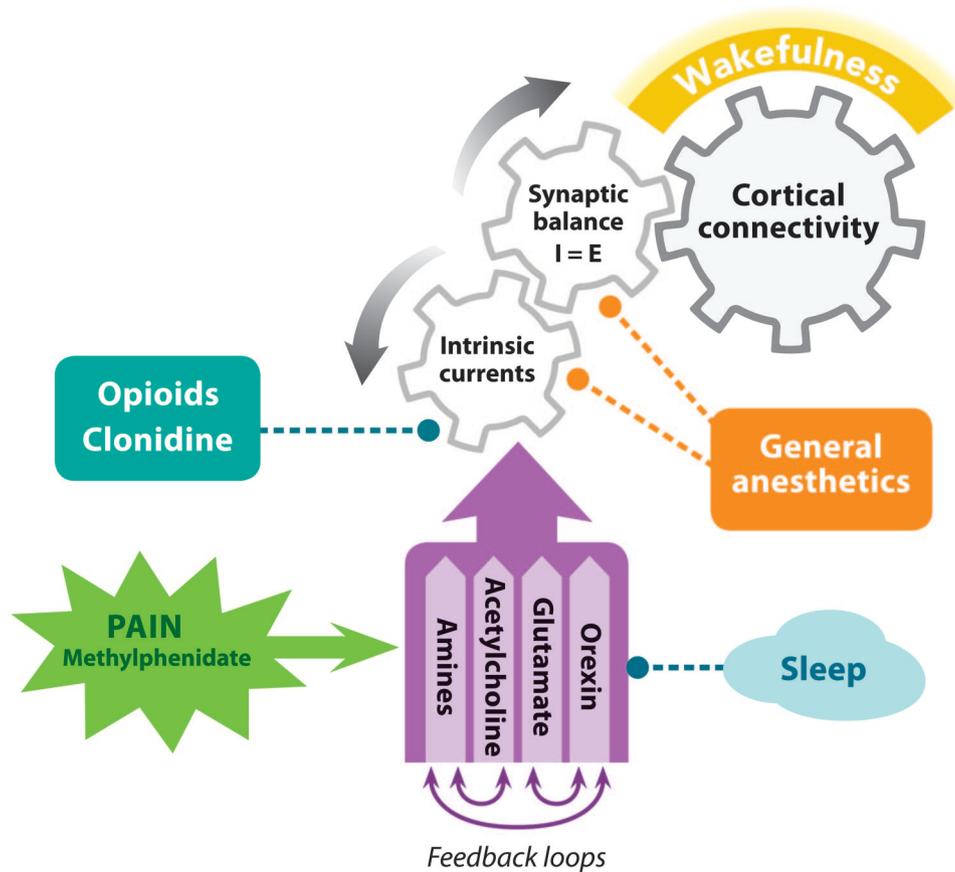


Fig. 1. A simplified diagram of the relationship between the various physiologic and pharmacological influences on waking. *Dashed lines and circles* indicate a suppressive effect. *Solid lines and arrows* indicate a stimulatory effect. The hypnotic effects of moderate doses of propofol can be overcome by increased intrinsic current modulation by methylphenidate. The increase in inhibitory synaptic effect with high concentrations of propofol is not directly antagonized by the methylphenidate, because it is acting on a different part of the system: the intrinsic currents. Thus methylphenidate is only a partial antagonist to propofol anesthesia. However, the full details of the interactions are more complex. For example, some of the analgesic effect of opioids is *via* an increase in aminergic tone, both in ascending and descending pathways. E = excitatory synaptic strength; I = inhibitory synaptic strength.

act, in the end, *via* some sort of final common pathway. Classically, redundant systems are characterized by parallel pathways of activation. However, the brainstem shows a more complex, web-like topology in which recruitment of one system helps recruit other arousal networks by a positive feedback mechanism, to achieve the critical level of neuronal activation required for the wakeful state (fig. 1).^{10–12}

In contrast, at high doses of general anesthetic, none of these wakefulness-inducing neuromodulators work. There is a ceiling on the antianesthetic effects of methylphenidate at about 0.8 minimum alveolar concentration or about 5 mg/l propofol. By definition, successful anesthesia implies the prevention of surgically induced arousal. If all it took to reverse general anesthesia were aminergic activation, then all the patients would regain consciousness when the surgeon cut them. This is also why specific antagonists to the various arousal systems (*e.g.*, antihistamine, anticholinergic, and antiadrenergic drugs) fail as anesthetic drugs. There is something special about anesthetic drugs. There is a point of no return where the concentration of anesthetic drug is suffi-

cient to reliably prevent waking, even in the presence of activation of these arousal systems. If we can explain this phenomenon, we are very close to understanding the core of general anesthesia.

The most parsimonious explanation of these observations is that consciousness requires a functional combination of both brainstem activation (*via* modulation of intrinsic neuronal currents) and also cortical synaptic responsiveness. Methylphenidate primarily acts on natural intrinsic neuronal currents strongly enough to antagonize moderate doses of anesthesia. But at higher doses, the “downstream” synaptic effects of anesthetic drugs are too great to be overcome by any amount of intrinsic current activation (including the pain from a surgical incision). Synaptic effects can trump intrinsic neuronal currents. In slow wave sleep, the dominance of inhibitory synaptic gain over excitatory gain is physiologically induced by neuromodulator withdrawal. Esser, Hill, and Tononi have coined the term “cortical block” to describe the mechanism of the resultant loss of consciousness.¹³ Cortical block prevents the formation of large-scale neuronal

assemblies that are believed to be a prerequisite for the conscious state. The same phenomenon of inhibitory-excitatory synaptic gain imbalance is even more apparent in theoretical models of anesthetic action.¹⁴ In natural sleep, the inhibitory synaptic amplification is secondary to the physiologic withdrawal of brainstem arousal neuromodulators, and therefore can be easily reversed by neuromodulator activation in response to internal and external stimuli. Unlike the situation of natural sleep, general anesthetic drugs (propofol or isoflurane) directly tip the balance in favor of inhibitory synaptic amplification – either by increased inhibition or decreased excitation – independent of the natural neuromodulators. This distorted and exaggerated negative feedback loop in the thalamocortical dynamics means that any pain-induced increase in neuronal activity will itself cause the anesthetic-induced, overly powerful, inhibitory feedback loop to act as a choke on high neuronal firing rates that might be induced by noxious stimuli. Hence, the work of Chemali *et al.* suggests a strategy to pull our patients back from the brink of anesthetic oblivion, but not from the depths of the “cortical block” abyss.

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