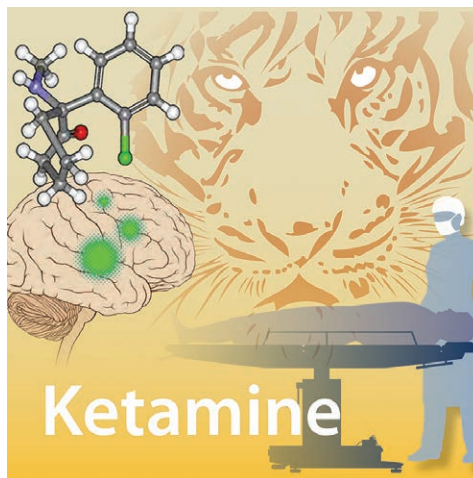


# Ketamine

## A Drug at War with Itself

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**K**ETAMINE has always been the odd one out. Like an eccentric uncle who always turns up at the holiday season with a new partner, ketamine has never really comfortably fitted in to simple classifications of anesthetic drugs.<sup>1</sup> Obviously, the anesthesia produced by ketamine is qualitatively very different, as compared to the more traditional  $\gamma$ -aminobutyric acid-mediated (GABAergic) hypnotics. Despite clear cardiopulmonary advantages (*i.e.*, minimal hypotension or hypoventilation), its use has waxed and waned for the past 50 yr, due to concerns over post-anesthetic neurocognitive behaviors. Currently, it is experiencing a minirenaissance and is increasingly used as an adjunct on top of the volatile-opioid-based anesthesia, for analgesic and antiinflammatory reasons. The interactions between ketamine and GABAergic hypnotics have not been thoroughly investigated. In this month's edition of ANESTHESIOLOGY, Hambrecht-Wiedbusch *et al.*<sup>2</sup> show that intraperitoneal ketamine changes the electroencephalogram from slow waves to a burst suppression pattern when given in a dose of about one sixth required for loss of righting reflex to rats, on top of 1.1 minimum alveolar concentration isoflurane. Paradoxically, when the isoflurane was stopped about 90 min later, the ketamine caused the rats to wake up twice as fast as the saline controls. Ketamine had both deepened the anesthesia and simultaneously speeded up emergence. Further, the investigators also measured the concentrations of acetylcholine in the extracellular fluid of the medial prefrontal cortex. They found that isoflurane caused a marked decrease in acetylcholine levels that was not immediately reversed by the ketamine. However, when the isoflurane was stopped, the acetylcholine concentrations in the ketamine-injected rats rapidly rebounded to double that of the controls—which supports the notion that this was the mechanism for the quicker recovery observed in the ketamine-treated animals.



***“...ketamine’s enigmatic effects reveal...that the one-dimensional universal concept of anesthetic depth is deeply flawed.”***

With the proviso that most humans are not simply larger rats, these results have some clinical implications, both for maintenance of anesthesia and for emergence. If we give ketamine as an adjunct to volatile or propofol anesthesia, can we still use the electroencephalogram as an indicator of adequacy of anesthesia? Will this ketamine wake the patient prematurely or prolong emergence? Our knowledge of the neuroscience underlying the dizzyingly complex pharmacodynamics of ketamine is still very incomplete, but we can understand these results in the context of known circuits in systems neuroscience.

It is well known that although ketamine has a direct myocardial depressant action, hypertension and tachycardia are common during its administration because of activation of the sympathetic nervous system. The plethora of ketamine’s conflicting central nervous system effects are in many ways analogous to this. Whereas ketamine’s use as a sole anesthetic has been hindered by the potential for patients to experience perceptual distortions in the recovery room<sup>3</sup>; in contradistinction, ketamine has also demonstrated potential as a neuroprotective agent to prevent or mitigate postoperative delirium.<sup>4</sup> Similarly, ketamine has been used both as an experimental model of psychiatric disease (*e.g.*, schizophrenia<sup>1</sup>) and as a proposed treatment for psychiatric disorders.<sup>5</sup>

From a neurosystems perspective, ketamine’s direct actions to antagonize excitatory glutamate neurotransmission and block other depolarizing currents (*e.g.*, hyperpolarization-activated cation channels) will tend to cause more thalamocortical hyperpolarization and hence the transition to a burst suppression pattern on the electroencephalogram—as observed by Hambrecht-Wiedbusch *et al.*<sup>2</sup> However, the few studies that look at the effects of ketamine when added to ongoing sevoflurane or propofol surgical anesthesia in

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humans suggest that there is either no change or some shift to higher frequencies. When given alone, ketamine causes a simultaneous increase in electroencephalogram power in both the low (delta or theta) and high (beta or gamma) frequencies.<sup>6,7</sup> As proposed by the authors, the most likely cause of these paradoxes is that fact that ketamine also activates a number of excitatory neuromodulators (amines and acetylcholine) that will cause thalamocortical depolarization, which is manifest as a loss of alpha activity and increase in beta and gamma activities. Much like stepping on the gas and brake pedal at the same time, if this amine and acetylcholine release is adequately suppressed by the anticholinergic actions of most volatile anesthetic drugs, the overall action of the added ketamine is the observed shift to a deep delta or burst suppression electroencephalographic pattern. Conversely, if the brain is still capable of activating aminergic and cholinergic responses, the indirect aminergic and cholinergic actions of ketamine will win out and cause a shift to higher frequencies, as is commonly seen in clinical practice, because such a state of brain aminergic activation is usual during the noxious stimulation of surgery and during emergence.

In conclusion, can we definitively say that clinicians should be aware of ketamine's potential to antagonize volatile general anesthesia? Not exactly. But we can be aware that not every anesthetic drug added to a patient's regimen will predictably decrease responsiveness in our patient. Perhaps, ketamine's enigmatic effects reveal what might be the most important that the one-dimensional universal concept of anesthetic depth is deeply flawed. The brain exists as a dynamical system, not as a seesaw.

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