Ketamine, a phencyclidine analog and dissociative anesthetic, has been used in anesthesia since the 1960s. Serial subanesthetic administration has been explored for treatment of depression and chronic pain; however, there has been a recent surge in its intraoperative and perioperative use among anesthesia providers. As ketamine becomes an important addition to multimodal acute pain regimens, it important that anesthesia providers review the physiologic underpinnings of ketamine administration. Herein, we review the primary scientific literature and discuss recent studies that have implicated ketamine in inflammation and oxidative stress, inhibition of ion channels in dorsal horn neurons, and in disruption of frontoparietal communication. Also discussed are the potential clinical implications these effects may have for patients.

Keywords: Frontoparietal communication, ketamine mechanism of action, mTOR, sodium/voltage-gated potassium channels.

Ketamine is a noncompetitive, N-Methyl-d-Aspartic acid (NMDA) glutamate receptor antagonist. It was initially developed in 1962 by Calvin Stevens, an organic chemist seeking to develop a structural analog of phencyclidine (PCP) with similar anesthetic potential but less emergence delirium. Since that time, the complex neuropharmacology of ketamine has been found to also affect non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, monoaminergic and opioid receptors, and voltage-dependent ion channels such as Na+ and L-type Ca2+ channels. Commercially available ketamine consists of a racemic mixture of 2 optical enantiomers, R(−) and S(+) and the preservative benzethonium chloride. When ketamine is used intraoperatively and perioperatively, the S(+) isomer produces less cardiac stimulation, less spontaneous motor activity, better analgesia, more rapid recovery, fewer psychotomimetic side effects, and decreased incidence of emergence delirium, whereas the R(−) isomer may be more potent with fewer side effects in the treatment of depression.

Used for more than a half century as an effective anesthetic and analgesic, ketamine has dissociative properties that elicit unique psychoactive effects. These effects include alterations in visual perception, out-of-body experiences, increased empathy, religious ecstasy, and transcendence of time and space. Negative side effects of ketamine include anxiety, panic, paranoia, and cognitive impairments. A lack of respiratory depression as well as analgesic properties, high bioavailability, fast time to maximum plasma concentration, large volume of distribution, multiple mechanisms of action, and hemodynamic stability make ketamine a favorable agent to use in Enhanced Recovery After Surgery (ERAS) pathways and has led to its increased intraoperative and perioperative use.

Interestingly, ketamine has also been shown to cause a transient activation of glutamate neurotransmission in the prefrontal cortex (PFC, referred to as a glutamate “surge”) and a sustained increase in PFC synaptic connectivity. This surge in glutamate causes hyperstimulation of neurons in corticolimbic brain regions and may be responsible for the schizophrenia-like symptoms experienced by some patients. For this reason, recent 2018 consensus guidelines consider active psychosis a relative contraindication to ketamine use in acute pain control. More conservative providers may elect not to use ketamine in patients with any psychiatric disorder or cognitive impairment. However, the physiologic effect of glutamate on NMDA receptors may vary depending on the location of the receptor. Synaptic NMDA receptors promote synaptic formation and neuronal survival, whereas extrasynaptic NMDA receptor activation leads to synaptic and neuronal death by altering nuclear calcium. At low doses, ketamine is thought to preferentially bind to and inhibit NMDA receptors on γ-aminobutyric acid (GABA)-ergic interneurons, decreasing their inhibitory effects on glutamate-releasing glutamatergic neurons. This disinhibition of glutamatergic neurons and increased depolarization of the presynaptic, glutamatergic neuron leads to a surge of glutamate release, as reported in the medial PFC.
tivates postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which conduct Na+ and Ca2+ into the cell. High local intracellular concentration of Ca2+ triggers the release of brain-derived neurotrophic factor into the synaptic space, which subsequently activates its surface receptor, tropomyosin receptor kinase B, which activates 2 downstream signaling cascades involving MEK-ERK and PI3K-Akt. These 2 pathways converge onto the mechanistic target of rapamycin (mTOR), which is a key regulator of neuronal protein synthesis, dendritic size and shape, and ultimately synaptic plasticity. These events lead to increased synaptic protein translation, in part through the suppressed phosphorylation of eukaryotic elongation factor 2 (eEF2). These newly synthesized proteins are inserted into the postsynaptic bouton, leading to further increases in AMPA receptor activation, dendritic spine density, and ultimately, increased synaptogenesis in key regions of the brain such as the PFC and limbic structures like the hippocampus and amygdala. This increased synaptogenesis may ultimately affect patients’ perception of acute pain and subsequently contribute to patients’ emotional affect and motivational drive during the postoperative recovery period. Improving the patient’s perception of pain can lead to earlier mobilization, decreased postoperative opioid use, and improved recovery.

Although ketamine has been shown to increase protein translation and long-term synaptic plasticity via the mTOR multieffector serine/threonine protein kinase pathway described above, different subanesthetic doses of ketamine have been shown to increase oxidative stress in the brain of rats. Therefore, the beneficial effects of increased synaptogenesis may be counteracted by increased oxidative stress and inflammatory cytokines when ketamine is administered to patients.

The goals of this review are to discuss (1) the literature further elucidating the neurophysiologic effects of ketamine after mTOR inhibition as an avenue to decrease the oxidative stress and inflammatory response associated with ketamine administration, (2) ketamine’s physiologic effects at the spinal cord level, and (3) the effects of ketamine on “feedback” connectivity. Reviewing these neurophysiologic mechanisms of ketamine will allow anesthesia providers to better understand the downstream effects of this medication based on the current literature, which can potentially lead to better administration and fewer adverse effects.

**Methods**

The literature presented in this review was selected from a comprehensive electronic search in the PubMed, MEDLINE, and Google Scholar databases through Albany Medical College’s Schaeffer Library. Key terms used for the search included ketamine and brain biology, molecular effects of ketamine anesthesia, effects of ketamine on the brain and spinal cord, ketamine effects on neural networks, and ketamine and neurobiology. Broad MeSH (Medical Subject Headings) terms and Boolean operators were selected for each database search. In addition, the same search terms were used to identify further relevant research. All research had to be completed within the past 13 years and was limited to publication in the English language. Both human and animal studies were included in the search. Three studies were chosen and are discussed in this literature review.

**Review of the Literature**

Ketamine is used frequently in ERAS pathways and as an analgesic adjunct in patients experiencing severe perioperative pain. However, prior murine research has shown that low-dose ketamine increases oxidative stress in brain tissue. Abelaira et al examined the behavioral and biochemical effects of ketamine in the murine PFC, hippocampus, amygdala, and nucleus accumbens after inhibition of mTOR signaling in the PFC to further elucidate the role of ketamine in inflammation and oxidative stress in the brain. Myeloperoxidase activity, thiobarbituric acid-reactive species (TBARS) formation, carbonyl protein formation, nitrite/nitrate concentration, superoxide dismutase activity, and catalase activity were measured from the brain tissue homogenates as markers of oxidative stress. Increased myeloperoxidase activity, TBARS formation, carbonyl protein formation, and nitrite/nitrate concentration are surrogates for increased oxidative stress, whereas superoxide dismutase activity and catalase activity are surrogates for protection against oxidative stress.

The results of the study by Abelaira et al were numerous. They found that ketamine at a dose of 15 mg/kg reduced the immobility time in rats. Although these findings have not been validated in human studies, these findings propose that ketamine use may actually help with early postoperative mobilization. Also, TBARS levels were increased in the PFC, hippocampus, and amygdala after ketamine administration, and nitrite/nitrate concentration was increased in all 4 brain regions of interest. Protein carbonyl content was increased in the PFC, amygdala, and nucleus accumbens after ketamine administration, and myeloperoxidase activity was increased in the hippocampus and nucleus accumbens. These findings suggest that perioperative ketamine use may increase oxidative stress in the brain. In attempts to help curb this inflammatory reaction, the authors administered the mTOR inhibitor rapamycin before ketamine injection and recorded the results. They found a statistically significant decrease in TBAR levels and nitrite/nitrate concentration in the hippocampus; decrease in nitrite/nitrate concentration, protein carbonyl content, and myeloperoxidase activity in the nucleus accumbens; and decrease in protein carbonyl content.
in the PFC. Both superoxide dismutase activity and catalase are enzymes that help protect against oxidative damage caused by reactive oxygen species, and ketamine was found to decrease the levels of both these protective enzymes in all 4 brain regions. Finally, there was a statistically significant increase in the tumor necrosis factor, an inflammatory cytokine involved in systemic inflammation, after administration of ketamine. Therefore, results of this study indicate that ketamine may cause an increase in both brain and systemic inflammation via 2 mechanisms: (1) increasing the amount of oxidative stress and (2) decreasing the brain’s ability to protect against oxidative stress.

Schnoebel et al.25 conducted a quantitative study to investigate the effects of the local-anesthetic-like actions of ketamine and its enantiomers on Na+ and K+ channels and their functional importance in intact rat dorsal horn neurons of laminae 1 through 3. The study found dose-dependent inhibition of Na+ current by ketamine in dorsal horn neuronal somata. Blockade was rapid in onset and readily reversible on washout. The S(+) ketamine enantiomer was significantly more potent than the R(−) enantiomer; illustrating stereoselective blockade of Na+ current. K+ currents were also recorded and studied. The total voltage-gated K+ current consists of inactivating A (K(A)) and delayed-rectifier (K(DR)) components. The study found that ketamine inhibited delayed-rectifier K+ current in a dose-dependent manner and that ketamine blocked delayed-rectifier K+ current to a greater degree than inactivating A K+ current. Lastly, the effects of ketamine on action potentials were seen with using concentrations as low as 30 μM of ketamine, with more profound effects with dose escalation. Ketamine was found to decrease all properties of single-action potentials, including action potential overshoot, maximum positive slope, maximum negative slope, and duration at 100-μM concentrations. The findings of this study help us understand the physiologic effects of ketamine administration in spinal blockade and help further explain the results of a prior study by Togal et al.26 In that prior study, S(+) ketamine, 0.1 mg/kg, with 7.5 mg of bupivacaine for spinal anesthesia provided adequate intraindividual effects, with shortened time-of-onset of motor and sensory block and decreased duration of analgesia. The authors found S(+)) ketamine to be an effective spinal blockade adjunct with particular local anesthetic effect when used with bupivacaine, as evidenced by decreased onset time, equivalent analgesic consumption and patient satisfaction, and no adverse hemodynamic effects.26

Lee et al27 conducted a prospective nonrandomized cohort study using electroencephalography (EEG) and normalized symbolic transfer entropy to assess directional connectivity across the frontal, parietal, and temporal regions of human surgical patients receiving ketamine, propofol, or sevoflurane. The ketamine portion of the study was conducted in 15 men and 15 women aged 22 to 64 years old, with ASA physical status class 1 or 2, who were scheduled for elective stomach, colorectal, thyroid, or breast surgery. Exclusion criteria included previous cardiovascular disease (including hypertension), a previous brain surgery, a history of drug or alcohol dependence, known neurologic or psychiatric disorders, and current use of psychotropic medications. Ketamine (2 mg/kg diluted in 10 mL of 0.9% normal saline) was infused over 2 minutes, and EEG and electromyography data were acquired until 5 minutes after loss of consciousness. The propofol and sevoflurane data were originally gathered for a previous study of the frontoparietal system by Ku et al.28 In their study, 8 men and 10 women aged 29 to 66 years old, with an ASA physical status 1 and 2, who were scheduled for elective abdominal or breast surgery were enrolled to receive either propofol (n = 9) or sevoflurane (n = 9) for general anesthesia induction while 8-channel electroencephalography data were recorded. Propofol was initially administered with a target-controlled infusion of 2.0 μg/mL and was increased at a rate 1.0 μg/mL per 20 seconds until loss of consciousness; sevoflurane was initially administered as 2 vol% and increased at a rate of 2 vol% per 20 seconds (up to 8%) until loss of consciousness. The data were aggregated and presented alongside the ketamine data for comparison.

The authors were interested in feedback and feedforward connectivity. Information feedback from the frontal cortex to other cortical regions is thought to mediate consciousness,29,30 whereas feedforward information flowing in the posterior-to-anterior direction is thought to mediate sensory processing, which can occur outside of consciousness.31,32 The authors found that the relative power of delta, theta, and gamma EEG frequency bands increased, but the relative powers of alpha and beta EEG frequency bands decreased after ketamine administration. The simultaneous increase of the relative powers for both slow waves (delta and theta) and fast waves (gamma) was unique to the ketamine administration. Propofol and sevoflurane varied from ketamine in that delta, theta, and alpha frequency bands increased, whereas beta and gamma frequency bands decreased after ketamine administration. The key finding was that ketamine reduced alpha power and increased gamma power compared with the opposite activity produced by propofol and sevoflurane. During administration of ketamine, feedback connectivity was gradually reduced and significantly inhibited after loss of consciousness, but feedforward connectivity was preserved. The asymmetry of information flowing in the frontal to parietal direction was also significantly reduced during ketamine injection and led to balanced information flow during the first minute after loss of consciousness. Although the asymmetry of information flowing in the frontal to temporal direction was also reduced, there still remained greater feedback connectivity in this
pathway. Therefore, inhibition of feedback connectivity in the frontotemporal network was not as robust as that of the frontoparietal network. In the comparison of ketamine, propofol, and sevoflurane, dominant feedback connectivity in the baseline state and the selective inhibition of feedback connectivity after induction was demonstrated among all 3 agents, yet feedforward connectivity was preserved. Therefore, the authors concluded that the reduction of feedback dominance and reduction of feedback/feedforward asymmetry in the frontoparietal network was a common neural correlate of anesthetic-induced unconsciousness across ketamine, propofol, and sevoflurane despite different mechanisms of actions and pharmacologic profiles. This is the first study showing a common biological mechanism for the loss of consciousness among all 3 anesthetic agents.

Discussion
Ketamine has been used clinically for more than 50 years. Its ability to act on glutamate receptors, nicotinic and muscarinic cholinergic receptors, monoaminergic and opioid receptors, and voltage-dependent ion channels such as Na⁺ and L-type Ca²⁺ channels has led to a continued evolution of our knowledge regarding its mechanisms of action and the downstream physiologic effects of its use. The 3 articles herein discussed help to further our understanding of ketamine physiology in the central nervous system.

A major limitation is that all 3 studies have small sample sizes. The study by Abelaira et al was conducted in 39 rats, the study by Schnoebel et al in 39 rat neurons and 52 rat somata, and the study by Lee et al in 30 human patients. The small numbers of these studies cannot allow readers to draw any definitive conclusions; rather they serve as investigative reports that can potentially lead to larger more highly powered studies. Furthermore, the physiologic data obtained from the studies by Abelaira et al and Schnoebel et al were from rats. Although this is a scientifically acceptable first step in the investigation of this physiology, the results should be validated in mammalian animal models to make the results more generalizable to human patients. It would be unethical to obtain human brain tissue, neurons, and somata simply to study an anesthetic’s mechanism of action, and therefore mammalian studies may be the next-best surrogate. Another limitation of these findings is the nonblinded, nonrandomized nature of all 3 studies. This could have led the findings to be influenced by measurement bias because the experimental groups were known to the researchers.

The work by Abelaira et al highlighted ketamine’s role in inflammation and oxidative stress and showed that the use of rapamycin, an mTOR inhibitor, could decrease the inflammatory and oxidative effects in some brain areas. However, although coadministration of rapamycin with ketamine may appear enticing to help improve patients’ outcomes by decreasing inflammation, the importance of the mTOR pathway in other areas of human biology may not allow for its inhibition in human patients. Activation of the mTOR pathway is involved in proliferation and clonal expansion of antigen-specific T cells, and inactivation of the pathway leads to detrimental immunosuppression. However, perhaps future studies can investigate administration of dexamethasone, a well-tolerated, clinically used anti-inflammatory agent, to patients receiving perioperative ketamine in an attempt to mitigate the oxidative stress and inflammation associated with ketamine administration.

The research by Schnoebel et al showed that ketamine blocks voltage-dependent sodium and delayed rectifying potassium channels in superficial dorsal horn lumbar neurons and somata at clinically relevant concentrations. Although the findings of this study are certainly interesting and present an explanation for the mechanism of action of ketamine when used as spinal blockade, we must remain wary of in vitro studies because the findings may not persist in vivo. Furthermore, ketamine is often combined with opioids when administered as a spinal blockade, and, therefore, the generalizability of these findings is limited when clinical practice patterns are taken into consideration.

The study by Lee et al is the first study to provide evidence for a common correlate between non-GABAergic (ketamine) and GABAergic (propofol and sevoflurane) anesthetics: the inhibition of frontal to parietal feedback connectivity with preserved feedforward connectivity. In addition to the study limitations already noted, the study assessed only external consciousness mediated by lateral frontoparietal networks and did not assess internal consciousness mediated by more medial networks. This is a limitation of the spatial resolution provided by 8-channel EEG and could be improved upon by future study designs using higher-resolution EEG recordings. Furthermore, the results of this study are limited to use of ketamine for induction, whereas many providers use ketamine as an adjunctive anesthetic agent. The effects of ketamine as an adjunctive agent in brain connectivity remain to be investigated and could differ from the results of this study. Finally, this study used normalized symbolic transfer entropy, a computational method based on information theory, to measure directional connectivity, which limits the ability to declare a true, causal interaction between brain regions.

Conclusion
The studies by Abelaira et al, Schnoebel et al, and Lee et al, although inherent with their respective limitations, contribute greatly to our understanding of ketamine physiology as a general anesthetic and local blockade agent. Abelaira et al found that ketamine increased myeloperoxidase activity, thiobarbituric acid-reactive species...
formation, carbonyl protein formation, and nitrite/nitrate concentration and decreased superoxide dismutase and catalase levels in certain parts of the brain. Schnoebel et al found ketamine to have dose-dependent inhibition of Na+ currents and delayed-rectifier K+ currents while decreasing frequency of action potentials in dorsal horn neurons. Finally, Lee et al found that ketamine increased relative power of delta, theta, and gamma frequency bands on EEG while decreasing the relative powers of alpha and beta frequency bands. They also found that ketamine reduced feedback connectivity and preserved feedforward connectivity.

The findings of these studies indicate that ketamine may contribute to inflammation and oxidative stress as well as disruption of frontoparietal communication when used in induction and general anesthesia. When ketamine is used for spinal blockade, it likely impairs excitability in superficial dorsal horn neurons by blocking sodium and voltage-gated potassium channels. Larger blinded, randomized studies of ketamine used as a perioperative adjunct are now needed to better understand ketamine’s physiologic effects when used in perioperative multimodal pain control.

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