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REVIEW

A Novel Application of Ketamine for Improving Perioperative Sleep Disturbances

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Abstract: Perioperative sleep disturbances are commonly observed before, during, and after surgery and can be caused by several factors, such as preoperative negative moods, general anesthetics, surgery trauma, and pain. Over the past decade, the fast-acting antidepressant effects of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine represent one of the most attractive discoveries in the field of psychiatry, such as antidepressant and anxiolytic effects. It is also widely used as a short-acting anesthetic and analgesic. Recent research has revealed new possible applications for ketamine, such as for perioperative sleep disorders and circadian rhythm disorders. Here, we summarize the risk factors for perioperative sleep disturbances, outcomes of perioperative sleep disturbances, and mechanism of action of ketamine in improving perioperative sleep quality.

Keywords: perioperative sleep disturbances, ketamine, antidepressant, anxiolytic, anti-inflammation

Introduction

The perioperative period refers to the duration from when the patient decides to receive surgery until the basic recovery period after surgery; this includes the time before, during, and after surgery. High sleep quality can accelerate incision healing, enhance immunity, and promote recovery and plays an important role in ensuring the quality of life of perioperative patients. However, due to numerous factors, patients can experience issues of varying degrees during the perioperative period.[1,2] A previous study reported that more than 40% of patients complained of poor sleep quality the first night before surgery and that their sleep problems usually last a few days after surgery.[3] Ruyi[4] compared the sleep conditions of perioperative patients and healthy volunteers and found that the incidence of sleep disturbances in perioperative patients was 17% higher than that in healthy volunteers. Preoperative negative moods, hormone levels, personality characteristics, general anesthetics, surgical trauma, and pain are all factors affecting sleep conditions and circadian rhythm in perioperative patients.[5–9] Long-term sleep disorders are closely related to many diseases, especially in elderly patients, such as chronic pain or pain sensitivity and postoperative cardiovascular events.[10,11] In addition, sleep deprivation caused by psychological problems may lead to neuronal apoptosis in cognition-related brain regions through neuroinflammation, changes in neurotransmitter activity (such as adenosine), and brain hypoxia or hypoperfusion injury.[12] The clinical use of the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine began in the 1970s. Since then, there has been increasing interest in ketamine for perioperative anesthesia, analgesia, and antidepressants.[13–15] Recent intensive research has shed light on new potential

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applications of this drug, such as for perioperative sleep disturbances and circadian dysregulation. Here, we summarize the risk factors for perioperative sleep disturbances, outcomes of perioperative sleep disturbances (Table 1), and mechanism of action of ketamine in improving perioperative sleep quality (Figures 1–3).

Risk Factors for Perioperative Sleep Disturbances

Effect and Mechanism of Preoperative Anxiety or Depression on Sleep Disturbances

Anxiety or depression of patients planning to undergo various surgical procedures has always been a concern for patients' health professionals. With over 312.9 million operations being performed each year worldwide,[16] the individual patient's perception of surgery and outcomes should be better assessed. It is estimated that between 25% and 80% of patients admitted to the hospital for surgery experience preoperative anxiety, which can negatively influence patient recovery.[17–19] Preoperative anxiety or depression has been recognized as a potential and preventable risk factor for postoperative complications. Changes in sleep neurophysiology are often observed in patients with depression. In many cases, sleep impairment is the main complaint of depression, which is often characterized by decreased sleep efficiency and a longer time of rapid eye movement (REM) sleep.[20,21] Moreover, preoperative sleep disturbances could enhance surgery-induced neuroinflammation, neuronal damage, blood–brain barrier disruption, and memory impairment 24 h after surgery, which may also cause or aggravate postoperative sleep disturbances and cognitive function.[22] However, the relationship between depression and insomnia is complex and bidirectional rather than a cause-effect relationship. The underlying mechanism between depression and sleep disturbances may be as follows: 1) Major depression is related to the interruption of REM. The transition to REM sleep is accompanied by a rapid decrease in monoamines and an increase in cholinergic tone.[23,24] The release disorder of these monoamine neurotransmitters that cause REM sleep abnormalities is also related to the manifestations of depression.[25] 2) The circadian rhythm is a 24-h physiological and behavioral rhythm controlled by the molecular clock in the suprachiasmatic nucleus. It plays an important role in regulating the sleep/wake cycle, including sleep duration, continuity, and structure. Biological clock imbalance is an important factor leading to insomnia and depression.[26–28] Many studies have identified a strong correlation between single nucleotide polymorphisms of clock genes and depression. For example, the single nucleotide polymorphism rs2287161 in cryptochrome may indicate a higher susceptibility to circadian dysregulation and major depression.[29,30] 3) A strong relationship has been observed between inflammation and depression. Inflammatory markers were reported to be higher in patients with depression than in those without depression. Furthermore, comorbid depression has been shown to be high in patients with inflammatory diseases. Sleep deprivation was confirmed to increase inflammatory markers (eg, interleukin-6 and C-reactive protein) through activation of the sympathetic nervous system and β-adrenergic signaling, which further promoted the occurrence and progression of depression.[31]

Effect and Mechanism of Intraoperative General Anesthetics on the Circadian Clock and Sleep

General anesthesia is a pharmacological state involving amnesia, immobility, unconsciousness, and analgesia. Its purpose is to deprive senses to prevent a motor response to stimuli and induce amnesia.[32] Two kinds of general anesthetics are widely used: halogenated gases (for example, halothane, desflurane, isoflurane, and sevoflurane) and intravenous anesthetics (for example ketamine, opioids, etomidate, and propofol). Most general anesthetics act on γ-aminobutyric acid $(GABA)_A$ receptors, and their mechanism and location of action in GABAergic transmission differ.[33] Ozone et al[34] showed that propofol anesthesia for 1 hour between 14:00 and 15:00 may cause the sleep structure of healthy volunteers to be disturbed at night after anesthesia. Sleep latency was significantly increased, and stage 2 sleep latency was significantly decreased. The sleep quality of children aged 4 to 6 months who use sevoflurane or propofol to repair cleft lip and palate surgery is also disturbed at night after anesthesia. The effect of propofol on sleep is more significant than that of sevoflurane.[35] The effects of general anesthesia on sleep might possibly be due to anesthesia-induced clock disruption.[36] Circadian rhythm and sleep quality dysfunction have harmful effects on mood, cognitive function, inflammation, and immune function.[37] Therefore, circadian rhythm disorders caused by general anesthesia may hinder postoperative recovery on multiple levels. This is potentially because 1) general anesthesia has a strong effect on the main neurotransmitter systems (such as GABA/NMDA) that are related to the control of circadian rhythms and may interfere with light entrainment of the clock. Since

Table 1 The Risk Factors and Consequences of Perioperative Sleep Disturbances

Risk Factors	Mechanisms	References
Preoperative anxiety or depression	The transition into REM sleep is accompanied by a rapid decrease in monoamines and a concomitant increase in cholinergic tone.	Pace-Schott EF et al[23] Wang YQ et al[24]
	A marked disruption in the circadian rhythm was observed in patients with MDD. Genes known to be crucial in the generation and regulation of circadian rhythm was found to be involved in depression. Clock genes dysregulation was assumed as an important factor associated with the development of both insomnia and depression.	Li JZ et al[26] Lamont EW et al[27] Satyanarayanan SK et al[28]
	In depressed patients, markers of inflammation have been shown to be higher than in non-depressed individuals, and in patients with an inflammatory disorder, comorbid depression has been shown to be high. Sleep loss may increase markers of inflammation (eg IL-6 and CRP) by activating the sympathetic nervous system and β-adrenergic signalling, which further promoted the occurrence and progression of depression.	Krysta K et al[31]
Intraoperative general anesthetics	General anesthesia has a strong effect on main neurotransmitter systems (such as GABA/NMDA) that are related to the control of circadian rhythms and may interfere with light-entrainment of the clock.	Brosnan RJ et al[38] Hummer DL et al [39]
	Expression of the core clock gene per2 is inhibited by general anesthesia (possibly via a NMDA/glycogen synthase kinase 3b (GSK3b) pathway). Four other studies describe a reduction in per2 expression following in vivo sevoflurane, dexmedetomidine or propofol treatment.	Kadota K et al[40] Anzai M et al[41] Ohe Y et al[42] Kobayashi K et al[43]
	Anaesthetics could act via the promotion of proteosomal degradation of BMAL1. Bellet et al found that ketamine inhibited per1 expression in vitro by preventing binding of the CLOCK:BMAL1 complex to the per1 promoter.	Bellet MM et al[44]
Postoperative pain	Chronic pain could dysregulate serotonergic raphe cells signaling, which would then contribute to prolonged sleep deprivation and greater disruption of sleep continuity. Due to the abundance of dopamine receptors in this region of the brain stem and the relationship between serotonergic and dopaminergic neurotransmission, pain-induced alterations in dopamine signaling may influence the raphe nuclei modulation of the sleep/wake cycle.	Foo H et al[52]
	Compromised pain inhibitory capacity has been demonstrated in many idiopathic clinical pain conditions with prominent sleep disturbance components. Opioid receptors are located in multiple nuclei that actively regulate both sleep and pain, including the preoptic suprachiasmatic nuclei, which controls sleep–wake cycles, and the periaqueductal gray, which plays a major role in descending pain inhibition. Moreover, sleep deprivation could also alter m- and d-opioid receptor function in mesolimbic circuits, diminishe basal endogenous opioid levels, and downregulate central opioid receptors.	Julien N et al[53] Staud R et al[54] Finan PH et al[55]
Consequences of perioperative sleep disturbances		
Neurodegenerative disease	Lack of sleep could increase Aβ peptides in the brain interstitial fluid, which had a direct relationship with wakefulness. Furthermore, injections of orexin, a major neuropeptide related to wakefulness, increased Aβ, whereas the orexin antagonist almorexant decreased Aβ levels.	Kang JE et al[60]
	Parkinson's disease dementia is caused by the aggregation of the protein α-synuclein, deposits of which are known as Lewy bodies (DLBs). Rapid eye movement sleep behavioral disorder is strongly associated with PD and dementia with DLBs.	Pringsheim T et al[62] Braak H et al[63]

(*Continued*)

Table 1 (Continued).

Risk Factors	Mechanisms	References
cogitive function	The consolidation of memory and normal brain functioning require high sleep quality, and sleep disturbance could interfere with the function of neuronal pathways, especially those of GABA and cAMP, which in turn impair synaptic plasticity. Poor sleep might contribute to neurodegeneration by causing neuroinflammation and disrupting neurogenesis, especially in the hippocampal areas, a key neuroanatomical region for learning and memory.	Diekelmann S et al[71] Stickgold R et al[72] Havekes R et al[73] Zhu B et al[74] Meerlo P et al[75]
	Increased sleep fragmentation and hypoxia are two consequences of disordered breathing during sleep, which may impair cognitive function. In animal models, hypoxia increased apoptosis and hippocampal atrophy through oxidative and inflammatory pathways.[76] Hypoxia increases the concentration of amyloid β, number of amyloid plaques, and tau phosphorylation in the brain, which are key components of Alzheimer's disease pathology.	Nair D et al[76] Gao L et al[77] Li L et al[78]
	Melatonin, a hormone associated with the sleep–wake cycle and produced by the pineal gland in a circadian manner, might be involved in another mechanism by which circadian rhythm dysregulation might contribute to cognitive impairment. Melatonin might have neuroprotective properties and is altered in patients with Alzheimer's disease. Therefore, changes in circadian rhythms and melatonin concentrations might occur before the onset of clinical symptoms and thus might serve as an early marker for risk of Alzheimer's disease and other dementias	Macchi, M.M et al[79] Pandi-Perumal, S.R et al[80] Ohashi, Y et al[89] Wu, Y. H et al[90] Zhou, J. N et al[91]

the retinal hypothalamic tract is NMDA receptor-dependent, isoflurane, sevoflurane, and ketamine are NMDA receptor antagonists,[38] which may inhibit hypothalamic retinal signal transduction, therefore inhibiting the optical entrainment of the biological clock. Continuous activation of GABA receptors can also change the clock phase and inhibit light-induced phase advances in rhythms.[39] 2) The expression of the core clock gene *per*2 is inhibited by general anesthesia (possibly through the NMDA/glycogen synthase kinase 3b pathway). Kadota et al found that administration of sevoflurane during the rising phase of the *per2* expression cycle resulted in lower *per2* mRNA levels in murine suprachiasmatic nuclei than in controls.[40] Consistent with the above findings, four other studies also described the decrease in *per2* expression after administration of sevoflurane, dexmedetomidine or propofol.[41–43] 3) Similar to the mechanism of sevoflurane-mediated inhibition of *per2*, Bellet et al found that ketamine was found to inhibit the expression of *per1* in vitro by preventing the binding of the CLOCK:BMAL1 complex to the *per1* promoter.[44] The histone acetyltransferase activity of CLOCK acetylates both histones 3 and 4, preventing CLOCK:BMAL1 binding to the *per1* promoter, which may result in a decrease in the level of acetylated histones in the promoter region. This will eventually lead to circadian dysfunction.[45]

Effect and Mechanism of Postoperative Pain on Sleep Disturbances

Although meaningful progress has been made in understanding pain mechanisms and the development of analgesics and anesthetics, postoperative acute pain control remains a challenge for approximately one-third of surgical patients.[46] A large Dutch cohort study of 1490 surgical patients who received postoperative pain treatment reported that patients still experienced moderate to severe pain on the day of surgery, which continued in 15% of patients at 4 days after surgery.[47] Acute postoperative pain is also accompanied by chronic pain, and 2–10% of postoperative patients experience severe pain.[48] Chronic pain is highly comorbid with sleep disturbances such as decreased total sleep time and increased sleep arousals.[49] The biobehavioral mechanisms of the association between sleep and pain are as follows: 1) dopamine is the principal neurotransmitter of the forebrain reward system and underlies the human behavioral drive to pursue pleasure. Dopamine is integral to the promotion and maintenance of arousal states and is intimately tied to the regulation of sleep and wake.[50,51] Foo and Mason theorized that chronic pain could dysregulate serotonergic raphe cell signaling, which would then contribute to prolonged sleep deprivation and greater disruption of sleep continuity. Due to the abundance of

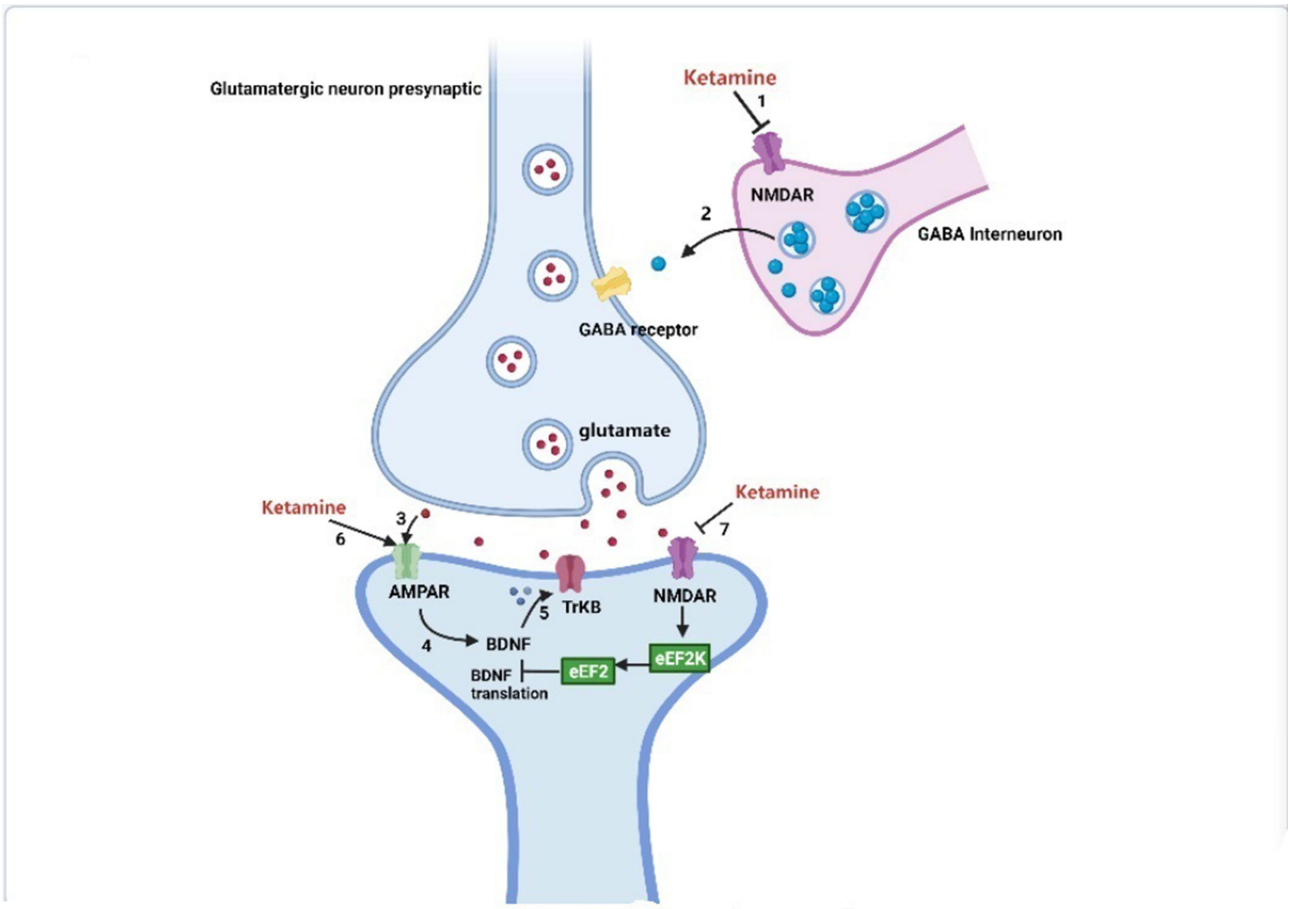

Figure 1 Antidepressant mechanisms of ketamine and potential biochemical biomarkers.

dopamine receptors in this region of the brain stem and the relationship between serotonergic and dopaminergic neurotransmission, pain-induced alterations in dopamine signaling may influence raphe nuclei modulation of the sleep/wake cycle.[52] 2) Previous studies have found that opioid peptides play a key mediating role in the downward pain regulation system. Studies have shown that prominent sleep disorders appear when the ability to inhibit pain is impaired.[53,54] Opioid receptors are located in multiple nuclei that actively regulate both sleep and pain, including the preoptic suprachiasmatic nuclei, which control sleep-wake cycles, and the periaqueductal gray, which plays a major role in decreasing pain inhibition. Moreover, sleep deprivation could also alter mu and delta opioid receptor function in mesolimbic circuits, diminish basal endogenous opioid levels, and downregulate central opioid receptors.[55]

Outcomes of Perioperative Sleep Disturbances

Perioperative Sleep Disturbances in Neurodegenerative Disorders

Neurodegenerative disorders are characterized by progressive loss of selectively vulnerable populations of neurons, which can be broadly classified by their clinical presentations, with extrapyramidal and pyramidal movement disorders and cognitive or behavioral disorders being the most common. Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) are three of the major neurodegenerative diseases.[56] Malhotra RK et al demonstrated that common sleep disturbances that may occur in most neurodegenerative conditions include insomnia, sleep apnea, restless

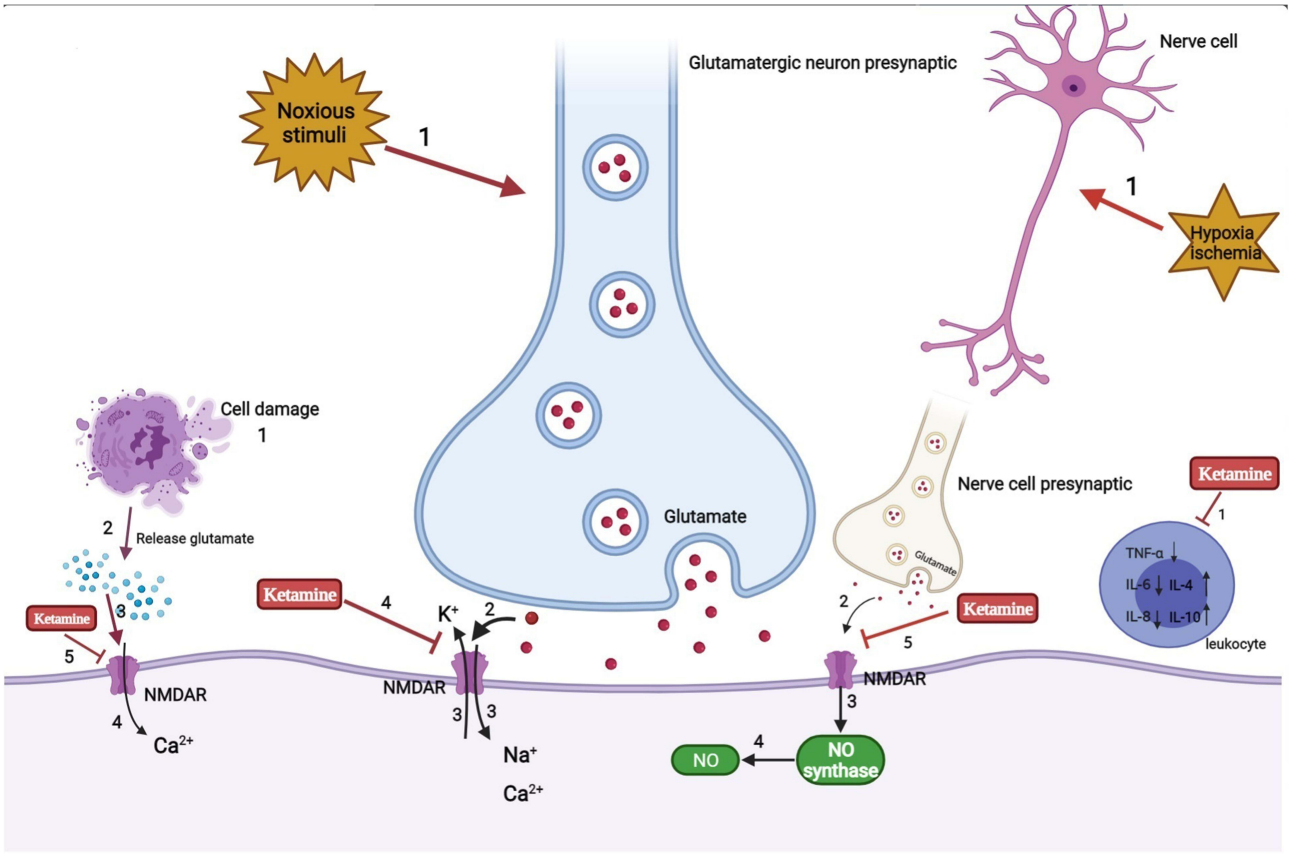

Figure 2 Analgesia and anti-inflammation mechanism of ketamine.

legs syndrome, and circadian rhythm disorders. Conversely, in terms of duration and quality, lack of sleep could also increase the neurodegenerative process and aggravate the underlying clinical condition.[57] Several studies have demonstrated that one night of sleep deprivation or interruption of nonrapid eye movement sleep in healthy volunteers may increase the levels of Aβ1-42 and Aβ1-40 in the cerebrospinal fluid.[58,59] In rats, lack of sleep could increase Aβ peptides in the brain interstitial fluid, which had a direct relationship with wakefulness. Furthermore, injections of orexin, a major neuropeptide related to wakefulness, increased Aβ, whereas the orexin antagonist almorexant decreased Aβ levels.[60] There may also be a significant relationship between sleep interruption and tau pathology. For example, tau protein metabolism and synaptic integrity were observed during sleep deprivation in a mouse model of AD.[61] In addition, PD is a progressive multisystem neurodegenerative disease that mainly affects people later in life. It is the second most common neurodegenerative disease in the world. With changes in population structure, its incidence and prevalence are increasing.[62] PD has unique neuropathic brain changes, whose formation of abnormal protein spheres is called Lewy bodies.[63] In patients with PD, both the sleep macrostructure (manifesting, for instance, as sleep fragmentation and a relative increase in superficial sleep) and sleep microstructure, manifesting as disturbed integrity of certain sleep stages (eg, disturbed sleep spindles and Kcomplexes, or insufficient muscle atonia during REM sleep), are affected.[64–66]

Perioperative Sleep Disturbances on Cognitive Function

In general, short-term total sleep deprivation has a deleterious effect across most cognitive domains, including attention, working memory, processing speed, short-term memory, and reasoning, with smaller effects on tasks of greater complexity.[67] There is increasing evidence that

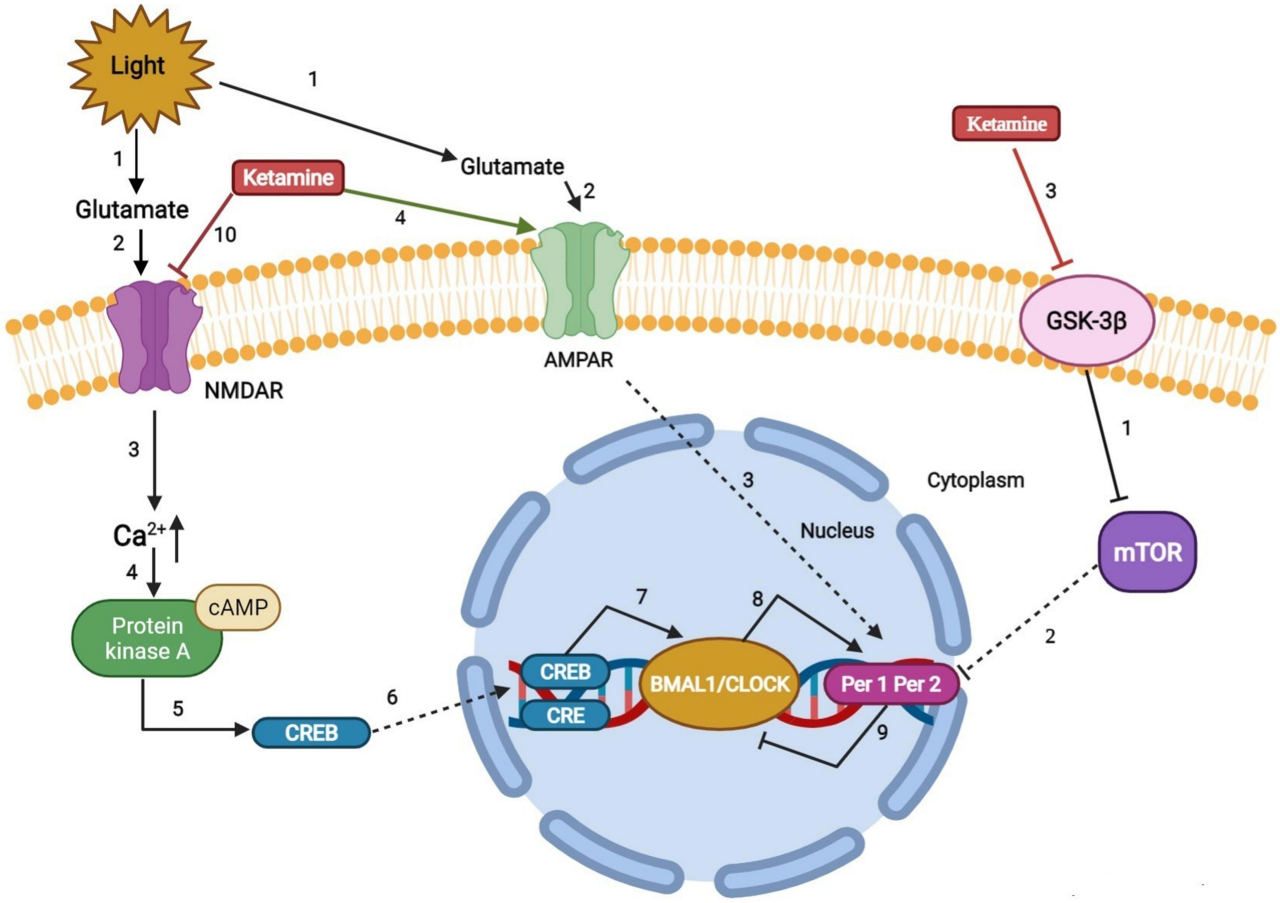

Figure 3 Regulation mechanism of ketamine on sleep and circadian system.

sleep time may predict cognitive outcomes in older adults.[68] Elderly women who reported a short sleep time were at an increased risk of cognitive impairment; however, there was no association with cognitive changes within 2 years, which may be due to the short follow-up time.[69] In addition, the circadian rhythm reflects changes in biological processes that oscillate and regulate several physiological processes in a 24-hour period, including sleep. In a prospective study of elderly women living in the community for more than 5 years, changes in circadian rhythms, such as decreased amplitude, less robust rhythm, and delayed peak activity, were all related to dementia or mild cognitive impairment.[70] Several mechanisms could explain the relationship between poor sleep quality and cognitive impairment. First, the consolidation of memory and normal brain functioning require high sleep quality,[71,72] and sleep disturbance could interfere with the function of neuronal pathways, especially those of GABA and cAMP, which in turn impair synaptic plasticity.[73] Poor sleep might contribute to neurodegeneration by causing neuroinflammation and disrupting neurogenesis, especially in the hippocampal areas, a key neuroanatomical region for learning and memory.[74,75] Second, increased sleep fragmentation and hypoxia are two consequences of disordered breathing during sleep, which may impair cognitive function. In animal models, hypoxia increased apoptosis and hippocampal atrophy through oxidative and inflammatory pathways.[76] Hypoxia increases the concentration of amyloid β, number of amyloid plaques, and tau phosphorylation in the brain, which are key components of Alzheimer's disease pathology.[77,78] Third, melatonin is a hormone produced by the pineal gland and related to the sleep-wake cycle. Renewed attention has been given to the role of melatonin in modulating behaviour, the immune system, and responses to stress, cancer and ageing.[79] Additionally, exogenous melatonin can affect circadian rhythm/sleep disorders, insomnia, cancer, neurodegenerative diseases, immune function disorders and oxidative damage.[80] Sedative, anxiolytic, anticonvulsant, antinociceptive and antidepressant actions have also been described.[81–84] Melatonin has been shown to increase the numbers of GABAA receptors and reduce 5-HT2A

receptor transmission, which may contribute to its antidepressant-like action.[85,86] In addition, it has been reported that melatonin levels are disturbed in some neurological conditions, such as stroke, AD and PD, which indicates its involvement in the pathophysiology of these diseases. Its properties qualify it to be a promising potential therapeutic neuroprotective agent, with no side effects, for some neurological disorders.[87,88] Clinically, many studies have reported that compared with healthy people, the level of melatonin in AD patients is reduced. After death, the level of melatonin in the CSF of the cerebral ventricle is negatively correlated with the Braak and modified Braak staging in the human cortex. Therefore, the level of melatonin is considered to be a marker of the progression of AD neuropathology. In the "preclinical" stages of AD Braak stages I and II, due to norepinephrine dysfunction and monoamine oxidase production, the melatonin circadian rhythm disappears.[89–91] In a transgenic rat model of Alzheimer's disease, long-term application of melatonin (approximately two months) reduced the deposition of immunoreactive antibodies in the hippocampus and cortex by 43% and 37%, respectively.[92] Melatonin in the active stage of disease progression can reduce amyloid deposition in the hippocampus (β1-42 and β1-40) and frontal cortex (β1-42), reduce hippocampal degenerative changes, prevent mitochondrial dysfunction, and delay anxiety and cognitive impairment in a sporadic rat model of Alzheimer's disease.[93] Therefore, changes in the circadian rhythm and melatonin concentration may serve as early markers for the risk of Alzheimer's disease and other dementias.

The Effects of Ketamine in Improving Perioperative Sleep Quality

The mechanisms by which ketamine improves sleep quality may be due to its antidepressant efficacy, anti-inflammatory properties, analgesic efficacy, interaction with the circadian system (Figures 1–3) and neurocognitive and anxiolytic effects.

Antidepressant Mechanisms of Ketamine and Potential Biochemical Biomarkers

Placebo-controlled trials have provided strong evidence for the rapid-acting (within hours) and sustained (lasting up to 7 days) antidepressant effects of a single administration of a subanesthetic dose of the noncompetitive NMDA receptor antagonist ketamine in treatment-resistant patients with depression.[94–96] Moreover, the antidepressant effects of ketamine have been demonstrated in many antidepressant-relevant tests in experimental animals.[97–99] The antidepressant mechanisms related to ketamine are listed as follows (Figure 1): 1) The cluster of electrical signals in the "anti-reward center" of the lateral habenula strengthened the inhibition of the "reward center" of the downstream cerebral monoamine nucleus, which causes depression. Blocking the cluster discharge of lateral habenular neurons can relieve the excessive inhibition of the "reward center" and play an antidepressant role. Cluster discharge of the lateral habenula depends on the NMDA receptor in the brain. Ketamine has long been recognized as a noncompetitive antagonist at NMDARs, which may explain its rapid antidepressant effects.[100,101] Ketamine can selectively block NMDA receptors expressed on GABA inhibitory interneurons, resulting in decreased activity of GABAergic interneurons and deinhibition of pyramidal neurons, which further increases excitatory neurotransmitter glutamate released from the synaptic cleft, activates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and increases the level of brain-derived neurotrophic factor.[102] 2) The changes in brain-derived neurotrophic factor levels caused by ketamine are related to its antidepressant effects, the increase in early sleep slow wave activity during nonrapid eye movement sleep, and the improvement of sleep quality in patients with treatment-resistant depression. Brain-derived neurotrophic factor is a well-known marker of depression, and the magnitude of increase has been shown to predict the acute mood response to ketamine.[103,104] The level of brain-derived neurotrophic factor depends on the regulation of eukaryotic elongation factor 2. Phosphorylated eukaryotic elongation factor 2 can inhibit the translation of brain-derived neurotrophic factor. Ketamine promotes the translation of brain-derived neurotrophic factors by reducing eukaryotic elongation factor 2 kinase activity and inhibiting the phosphorylation of eukaryotic elongation factor 2. Tropomyosin-related kinase B is the receptor of brain-derived neurotrophic factor, and activation of the brain-derived neurotrophic factor-tropomyosin-related kinase B pathway plays an important role in the treatment of depression.[105,106] 3) AMPAR is an ionotropic glutamate receptor responsible for rapid synaptic nerve conduction. Ketamine can either directly activate AMPAR or indirectly activate AMPAR by antagonizing NMDA receptors to promote the release of glutamate, which has antidepressant effects. After ketamine activates AMPAR, it causes the opening of L-type voltage-dependent calcium ion channels, stimulates the release of brain-derived neurotrophic factor, and enhances its antidepressant effects.[107] 4) Ketamine rapidly activates the mammalian target of rapamycin (mTOR)

pathway, leading to an increase in synaptic signaling protein in the prefrontal cortex of rats and an increase in the number and function of new spinous synapses, which represents the mechanism of rapid antidepressant effects of ketamine. In addition, in the depression model, the blockade of mTOR signaling completely blocked the induction of synaptic and behavioral responses by ketamine.[108] 5) Ketamine may significantly increase the release of monoamine transmitters in the central nervous system, promote angiogenesis and synaptic regeneration, and enhance neuronal activity, which may be associated with its antidepressant effects.[109,110]

Analgesia and Anti-Inflammation Mechanism of Ketamine

The use of ketamine has been limited due to its psychodysleptic effects. At first, it was mainly used for anesthetic purposes. After United States Food and Drug Administration approval in 1970, ketamine began to be used for analgesic purposes.[111] Human studies have reported that adding ketamine to opioid treatment of acute pain can prevent opioid-induced respiratory depression and hyperalgesia.[112] Using the smallest dose of S-ketamine during perioperative anesthesia, lower than normal low-dose racemic ketamine, could reduce postoperative opioid consumption and hyperalgesia and reduce the risk of postoperative delirium.[113] The use of esketamine in the perioperative period can relieve pain by 20% ~25% at 48 h after surgery while reducing the total dosage of analgesics required by 30%~50%, reducing the adverse effects experienced by patients, such as nausea and vomiting.[114] The potential mechanism may be as follows (Figure 2): 1) The emergence of noxious stimuli causes the release of the nerve presynaptic membrane excitatory transmitter glutamate. Then, activation of the NMDA receptor in the central and peripheral nervous systems causes voltage-dependent sodium and calcium ions to enter the cell and potassium ions to exit the cell. As a noncompetitive antagonist of NMDA receptors, ketamine blocks the transmission of glutamate by shortening the opening time of these receptor channels and reducing the frequency of receptor channel opening, thereby exerting anesthetic and analgesic effects. In addition, ketamine also induces a sustained blocking effect by reducing the rate of separation from the receptor.[115] 2) NO is an important factor in tissue damage and inflammation. Hypoxia and ischemia can activate NMDA receptors to produce NO. Ketamine can reduce the production of NO by inhibiting NO synthase, thereby inhibiting inflammatory pain.[116] 3) In the case of ischemia, hypoxia, and trauma, nerve cells release a large amount of excitatory amino acids such as glutamate, which act on NMDA receptors and cause nerve cell damage. Ketamine can inhibit the activation of NMDA receptors and reduce the concentration of glutamate to protect nerve cells. Cell injury also leads to the release of excitatory amino acids that bind to the receptor, resulting in a large concentration of calcium ions entering the cell. Ketamine blocks the NMDA receptor, thereby stabilizing intracellular calcium ion levels and inducing neuroprotective effects.[117] 4) Ketamine can inhibit the activation of leukocytes during the inflammatory response, reduce the production of inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-8, and stimulate the secretion of anti-inflammatory factors such as interleukin-4 and interleukin-10 to relieve the nerve damage caused by inflammation.[117]

Regulatory Mechanism of Ketamine on Sleep and the Circadian System

REM reduction, slow wave sleep, and sleep fragmentation are important clinical biomarkers of perioperative sleep disturbance and circadian rhythm asynchrony.[118] Given the beneficial effects of ketamine on sleep, an early rat study showed that ketamine stimulates slow-wave activity during non-REM sleep.[119] The results of Ahnaou et al further extend these observations. In particular, ketamine prolongs the average duration of deep sleep, indicating that deep sleep is maintained and consolidated.[120] In addition, ketamine-induced brain-derived neurotrophic factor, a modulator of neuroplasticity, induced stage N3 sleep.[121,122] Furthermore, data from human, animal, and neuronal cell studies also suggested that low-dose ketamine can modulate circadian rhythms by regulating clock genes.[123] These findings suggest that the rapid antidepressant effect of ketamine may also be related to its effect on clock gene-related molecules, leading to changes in the circadian timing of the central clock and/or its effect on the entrainment circuit that synchronizes the central clock with the external light cycle.[103] The possible reasons may be as follows (Figure 3): 1) ketamine's effects on circadian rhythms include attenuating phase-shifting responses to light, altering the diurnal rhythms of the widespread NMDA receptors and AMPARs in the suprachiasmatic nucleus, and increasing the expression of the core clock genes *per1* and *per2* via its actions on glutamate receptors.[124] 2) Recent work has implicated mammalian target of rapamycin as a potential site for

ketamine's rapid antidepressant actions. Glycogen synthase kinase 3β is a potent inhibitor of mammalian target of rapamycin C1 (rapamycin complex 1). Blocking mammalian target of rapamycin significantly attenuates the light-induced expression of the circadian PER1 and PER2 proteins. Furthermore, rodent studies demonstrated that inhibition of glycogen synthase kinase 3β may play a role in the antidepressant actions of low-dose ketamine.[125–129] 2) Ketamine downregulates the period circadian regulator 2 gene by changing its inhibitory actions on the heterodimer CLOCK/BMAL1. In addition, ketamine can alter the Notch signaling pathway and the MAPK signaling pathway, which responds to excitatory glutamatergic signaling that controls synaptic plasticity and higher brain processes.[130] 3) The lateral habenula is a region of the brain connected with the suprachiasmatic nucleus and could be a potential candidate for the circadian effects induced by ketamine. The lateral habenula appears to function as an individual circadian oscillator in the central nervous system. In particular, it exhibits inhibitory control over connecting dopaminergic, noradrenergic, and serotonergic areas. The increased activity of lateral habenular nucleus neurons may promote stronger inhibitory control in these areas and have a negative impact on mood regulation. A recent rodent study showed that the burst activity of lateral habenular neurons in depressive animals increased, and ketamine reversed this phenomenon.[131] Moreover, Kushikata T et al also found that ketamine and propofol had opposite effects on the activity of the sleep–wakefulness-related endogenous substances orexin (OX) and melanin-concentrating hormone (MCH). Ketamine has a greater effect on OX activity during the perianaesthetic period, while propofol causes a greater increase in MCH activity after the anaesthesia period and has a smaller effect on OX activity. These differences are related to the different effects of the two drugs on the sleep structure after anaesthesia. Ketamine immediately enhanced wakefulness after anesthesia on the first day after anesthesia, and NREMS rebounded. Their research shows that anesthetics can affect various sleep-related endogenous substances; however, the modulation mode may depend on the type of anesthetic. In other words, the process of sleep disturbance after anesthesia may be drug-specific.[132]

Neurocognitive and Anxiolytic Effects of Ketamine

Major depressive disorder (MDD) is the most common mental disorder, affecting more than 16% of adults throughout their lives. Although standard antidepressant treatment is usually effective, approximately 30% of MDD patients do not respond adequately to established medications, psychotherapy, or physical therapy, which may be because symptoms of MDD, such as low mood, anhedonia, cognitive dysfunctions and somatic manifestations, are very heterogeneous.[133] Convincing reports indicate that the most important susceptibility factors for MDD are chronic stress and hypothalamic–pituitary–adrenal (HPA) axis dysfunction. Although the mechanisms by which glucocorticoids contribute to depressive symptoms have not been entirely established, strong pieces of evidence have reported that chronic exposure to glucocorticoids causes structural defects in the dentategyrus (DG) area of the hippocampus, including reduction of dendritic arbor and spine density, concomitant with the onset of depressive symptoms.[134] An animal study by Fraga DB et al showed that ketamine can reverse corticosterone-induced loss of dendritic branches in the ventral and dorsal DG regions, which are associated with mood regulation and cognitive function, respectively. This study provides new evidence that a single dose of ketamine can rescue the damage to glucocorticoid receptors and dendritic branches in the hippocampus of mice receiving chronic corticosterone administration. These effects may be related to their rapid antidepressant response.[135] In addition, a single dose of S-ketamine, instead of R-ketamine, can cause the loss of paralbumin (PV)-positive cells in the medial prefrontal cortex and the anterior DG area.[136] Moreover, anxiety disorders, currently the most prevalent psychiatric disorder, cause a high social impact and economic burden.[137] They are often comorbid with major depressive disorder, which has an overall rate of 50–60% for the occurrence of any anxiety disorder. Patients with anxious forms of depression are more likely to have severe depressive symptoms, including fatigue, thoughts of guilt, and worthlessness, and are more resistant to treatments.[138] Recent literature proves that ketamine may be a potential treatment option for patients with refractory generalized anxiety disorder/social anxiety disorder. A subanesthetic dose of ketamine induces anxiety with a long lasting time in 12 patients (up to 1 week).[139–141] Animal models also show different dose-dependent effects of ketamine on cognition, depression, and anxiety. The main hypothetical mechanism is to change BDNF levels. Subanaesthetic doses of ketamine are considered to have a positive effect on the level of BDNF in the hippocampus. Wu C et al found that a single infusion of subanaesthetic doses of ketamine (0.5 mg/kg) increased hippocampal volume (usually a representative of increased BDNF). This is also true in a small group of MDD patients who are not receiving

medication.[142] An animal study confirmed that an anesthetic dose reduced BDNF expression in the hippocampus, correlating with depressive-like behaviors, anxiety-like behaviors and cognitive impairment.[143] Human studies have shown that infusion of higher analgesic doses (8–20 mg/h) in healthy volunteers also shows significant cognitive deficits, which indicates that acute ketamine is potentially dose-dependent on cognitive and cognitive symptoms.[144] Despite this, several studies have shown that the dose of anesthetics obviously lacks any form of long-term side effects, and the dose of subanesthetics seems to have a very low risk in clinical trials.[145] de Souza I et al's study also demonstrated that a single injection of ketamine can cause impaired episodic memory, but this may be an acute finding and not related to long-term cognitive dysfunction.[146] Another recent study on intranasal esketamine administration in healthy volunteers showed that there was significant cognitive dysfunction at 40 min, but no cognitive dysfunction was found at 2, 4, and 6 h postdose.[147] In conclusion, the dose of ketamine used to treat resistant depression seems to have an overall cognitive effect, which may be the basis of its rapid effectiveness. The negative cognitive side effects of ketamine may appear transiently during acute administration of ketamine but only persist when ketamine is used in large quantities for a long time and appear to be reversible.

Conclusions and Future Directions

Perioperative sleep disturbances are commonly observed before, during, and after surgery. They are usually ignored and may increase the risk of postoperative neurocognitive disorders. Thus, improving perioperative sleep may reduce the incidence of postoperative delirium and postoperative cognitive dysfunction. Ketamine, as a nonselective, noncompetitive antagonist of the NMDA receptor, has made remarkable progress in the last 5 years in terms of identification of the molecular and cellular mechanisms critical to its rapid antidepressant effects. In particular, combining two markers of synaptic plasticity, brain-derived neurotrophic factor levels and EEG sleep slow waves, was demonstrated to be an effective approach for identifying ketamine's capacity to increase synaptic strength. Meanwhile, ketamine could also improve symptoms of anxiety in patients with treatment refractory generalized anxiety disorder or social anxiety disorder who are not currently depressed and is safe and well tolerated. Recent intensive research has shed light on new possible applications of this drug. As indicated in this review paper, studies on the mechanism of action of ketamine in improving perioperative sleep quality have resulted in some interesting findings worthy of further research. Further research is needed to identify other signs of plasticity and expand emotional responses.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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