



Effects of ketamine on EEG in baboons with genetic generalized epilepsy

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ABSTRACT

Ketamine, a noncompetitive N-methyl-D-aspartate receptor (NMDAR) antagonist, used as an anesthetic has been reported to induce seizures both in humans and baboons predisposed to epilepsy. In this study, we aimed to characterize the acute effects of ketamine on scalp (sc-EEG) and intracranial EEG (ic-EEG) in the baboon, which offers a natural model of genetic generalized epilepsy (GGE). We evaluated the electroclinical response to ketamine in three epileptic baboons. The raw EEG data were analyzed within 10 min of intramuscular ketamine (5–6 mg/kg) administration. Earliest EEG changes occurred after 30 s in sc-EEG and after 15 s in ic-EEG of ketamine administration. These initial changes involved increased paroxysmal fast activity (PFA) followed by slowing, the latter emerging first occipitally, and then spreading more anteriorly. Generalized spike-and-wave discharges (GSWDs) were evident on both sc-EEG and ic-EEG within two minutes, but focal occipital discharges were already increased on ic-EEG after 15 s. Occipital slowing emerged on ic-EEG after 30 s, before spreading fronto-centrally and orbito-frontally. By 60–120 seconds post-injection, ic-EEG demonstrated a parieto-occipital burst suppression (BS), which was not noted on sc-EEG. Ketamine waves and seizures, especially if the latter were subclinical, also appeared earlier on ic-EEG. This study highlights the anesthetic and proconvulsant effects of ketamine originate in the occipital lobes before fronto-central regions. We speculate that NMDAR concentration difference in cortical regions, such as the occipital and frontal cortices, are mainly involved in the expression of ketamine's EEG effects, both physiological and epileptic.

1. Introduction

Ketamine is a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist used in humans and animals for sedation and restraint (Wright, 1982). At low doses of 1–2 mg/kg intravenously, or 4–6 mg/kg intramuscularly, ketamine causes dissociation, during which patients are arousable but unresponsive with substantial alleviation of pain and transient amnesia (Modica et al., 1990). The dissociative effect is maximal after one minute of intravenous injection and five minutes of intramuscular administration. As muscle tone is maintained or even increased (catalepsy), blood pressure is elevated and respiratory drive is increased. Patients do not require intubation. These features, in addition to its short half-life, make it an attractive agent for short-term anesthesia. Nonetheless, because of proconvulsant effects, psychotic symptoms associated with emergence from anesthesia and its abuse potential, ketamine lost its popularity (Greifenstein et al., 1958; Kohrs and Durieux, 1998; Domino and Luby, 2012). Recently, ketamine employed at subanesthetic doses of 0.1–1 mg/kg, has re-emerged as a promising treatment for several psychiatric and behavioral disorders, including major depressive disorder, post-traumatic stress disorder, and

even for chronic pain syndromes (Feder et al., 2014; Lee and Lee, 2016; Sanacora et al., 2017). Ketamine has also been shown to be an efficacious agent in the treatment of super-refractory status epilepticus in adults and children in several studies (Rosati et al., 2012; Gaspard et al., 2013; Synowiec et al., 2013; Fang and Wang, 2015).

Ketamine's effect on seizure is both dose- and time-dependent (Celesia et al., 1975). While ketamine's inhibition of the postsynaptic NMDARs should lead to the disruption of increased glutamatergic activity during seizures, inhibition of presynaptic NMDARs on glutamatergic neurons as well as post-synaptic receptors on inhibitory interneurons, leads to temporary suspension of negative feedback loops, resulting in increased glutamate secretion and excitation (Moghaddam et al., 1997). In addition to the immediate effects on glutamate transmission, long-term effects via enhancement of non-NMDA glutamatergic, such as α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), as well as serotonergic and dopaminergic neurotransmission, are likely to be responsible for the adverse and beneficial behavioral effects. At low doses, ketamine lowers the seizure threshold within minutes of administration in people with predisposition to focal epilepsy (Ferrer-Allado et al., 1973; Celesia et al., 1975). This effect has

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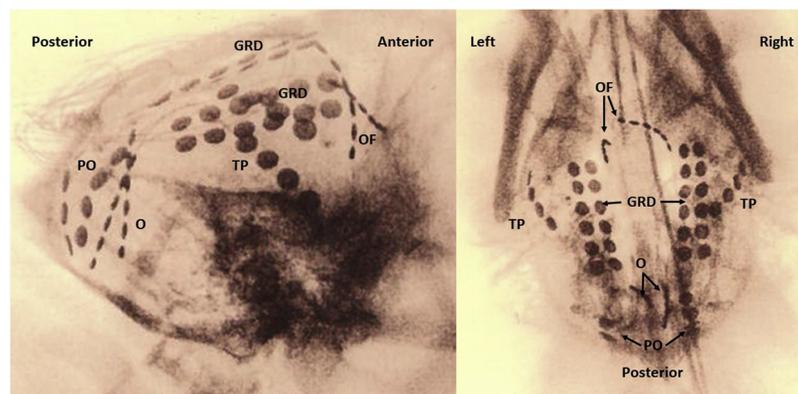


Fig. 1. Electrode Map in B3.

Legend: OF (orbitofrontal depth electrodes, GRD (frontoparietal grid electrodes), TP (temporoparietal strip electrodes), PO (parietooccipital strip electrodes) O occipital depth electrodes).

not been documented in humans with idiopathic generalized epilepsies, particularly not with intracranial EEG (ic-EEG) recordings, as such examinations are not clinically justified.

For this reason, our group evaluated the ketamine effect in a natural animal model of genetic generalized epilepsy (GGE), the epileptic baboon (Szabó et al., 2005, 2012a; Szabó et al., 2013). The epileptic baboon suffers from myoclonic seizures (MS) and generalized tonic-clonic seizures (GTCS) and exhibits generalized ictal and interictal epileptic discharges (IED) on scalp EEG (sc-EEG) and ic-EEG. Similar to juvenile myoclonic epilepsy in humans, photosensitivity, i.e. the propensity to provoke seizures with visual stimuli, is also prevalent in this model (Szabó et al., 2005, 2013). Due to ketamine's dissociative properties and short half-life, along with its ability to activate ictal and interictal epileptic discharges without suppressing photosensitivity, at low doses, it has been extensively employed during sc-EEG and ic-EEG as well as neuroimaging evaluations in the epileptic baboon (Szabó et al., 2013, 2012b; Szabó et al., 2008). In this study, we compare the effect of ketamine between sc-EEG and ic-EEG in epileptic baboons and characterize electrophysiological mechanisms underlying its anesthetic and proconvulsant effects.

2. Material and methods

This study was approved by the Institutional Animal Care and Use Committees of the University of Texas Health Science Center at San Antonio and the Texas Biomedical Research Institute. All baboons were housed at the Southwest National Primate Research Center at the Texas Biomedical Research Institute and treated in accordance with the “Guide for the Care and Use of Laboratory Animals” (Institute for Laboratory Animal Research, 2011) and the Animal Welfare Act (Animal Welfare Act as Amended, 2008). Three adult baboons (2 females and one male, mean age 7, range 4.5–10 years old) belonging to *Papio hamadryas anubis* or hybrid species, were evaluated with sc-EEG and subsequently implanted with subdural grids, strips and depth electrodes for invasive video-EEG monitoring for a mean 15 (range 11–21) days. Scalp EEG and intracranial implantation techniques have been described in detail in our prior studies (Szabó et al., 2005, 2012b).

Scalp EEG recordings were performed in the baboons after their transfer into a primate chair. The baboons were sedated with intramuscular S-ketamine 5–6 mg/kg (Ketaved, Phoenix Scientific, St. Joseph, Missouri) for light sedation prior to transfer from cage to primate chair. Their scalps were shaved, and gold cup electrodes were applied with electrode paste and fixed with small squares of tape soaked in collodion. The surface electrodes were placed according to the standard international 10–20 electrode placement system at the FP1, FP2, T4, C4, Cz, C3, T3, O1, O2, and A2 positions. Lateral eye movements were recorded with electrodes placed next to the eyes

(EOG1 and ECOG2) and muscle activity from deltoids bilaterally. A single electrode was placed over the anterior chest wall to monitor the heart rhythm. Photic stimulation was delivered on two occasions 15 min apart, the first time while the baboon was unresponsive, the second time, when it was able to visually track movement despite drug-induced nystagmus. A second ketamine dose was given before the study was discontinued, and the EEG effects of ketamine were monitored for 10 min. The sc-EEG studies lasted 45–60 minutes in duration.

Implantation of intracranial electrodes was performed in all three baboons (45–61 contacts). Two baboons (B1, B2) were included in a prior study (Szabó et al., 2012b), while one baboon (B3) was implanted at a later date. Baboons were sedated with ketamine and diazepam and maintained on isoflurane with MAC of 1.5–2% after intubation during the electrode placement. To avoid the risk of increase in intracranial pressure, the animals were hyperventilated to a pCO₂ below 30 mm Hg and pretreated with mannitol. Subdural strips and grids were implanted bilaterally through symmetrical craniotomies over the fronto-parietal, parieto-occipital and temporo-occipital regions. Two 1 × 4 depth contacts were placed in orbitofrontal regions in all three baboons, and mesial occipitally in B3 (Fig. 1). Postoperative skull X-rays were obtained to verify electrode placement. After extubation, the baboons were monitored in the veterinary intensive care unit from 1 to 5 days. The effects of ketamine on ic-EEG were also evaluated after two doses, the first given prior to the transfer from cage to primate chair for a single trial of photic stimulation followed by electrocortical stimulation, and the second when they were returned to their cages (Szabó et al., 2012b). Simultaneous sc-EEG and ic-EEG recordings were obtained during photic stimulation in one baboon (B2). All sc-EEG and ic-EEG recordings were performed using Neurofax 9200 (Nihon-Kohden, Japan). Bipolar montages were utilized for recording and review of EEG data. The EEG data and video recordings were reviewed separately by the authors (SG and CAS), both board-certified in Clinical Neurophysiology and Epilepsy.

3. Results

Table 1 summarizes the results of the electroclinical data. Baseline sc-EEG showed sporadic, at times periodic generalized IEDs, and clinical seizures consisting of MS, tonic and GTCS. The ic-EEG showed generalized and multifocal IEDs, the latter predominantly in the parieto-occipital regions, as well as focal subclinical seizures originating in the parieto-occipital regions more often, than frontally. The GTCS were generalized in onset, with a parietal or frontal maximum.

3.1. Scalp EEG

Initial EEG changes were noted only after 30 s, consisting of

Table 1
Composite of Ketamine-induced Scalp and Intracranial EEG Changes in Epileptic Baboons.

EEG	15–30 s	30–60 s	60–120 s	2–5 min	5–10 min
ScEEG	1. No change	1. Generalized 30-40 Hz Fast Activity	1. Continuous 3-5 Hz slowing, O then FC 2. Increased SWC, GEN	1. Paroxysmal fast activity 20-25 Hz, 2. Ketamine waves 3. Ketamine-induced seizures (only clin)	1. Paroxysmal fast activity 20-25 Hz, 2. Ketamine waves, resolving 3. Ketamine-induced seizures
IcEEG	1. FC 20-25 Hz activity 2. Spikes, bilateral O	1. FC 30-40 Hz activity 2. Continuous 3-5 Hz slowing, first O, then C or OF	1. FC 30-40 Hz activity 2. Ketamine waves 3. SWC, GEN, mainly FC/OFF 4. BSuppr Occ	1. Paroxysmal fast activity 30-40 Hz 2. Ketamine waves 3. Ketamine-induced seizures (clin and subclin)	1. Paroxysmal fast activity 30-40 Hz, spreading to O 2. Ketamine waves, resolving 3. Ketamine-induced seizures

Legend: Sc-EEG (scalp EEG), Ic-EEG (intracranial EEG), FC frontocentral, O(ccipital), C(entral), OF orbitofrontal, SWC (spike-and-wave complexes), GEN(eralized), BS burst suppression.



Fig. 2. Ketamine Effect on Interictal Scalp EEG.
Legend: FP frontopolar, T(emporal), O(ccipital), C(entral), Lt eye (Left epicanthus), Rt eye (Right epicanthus), Arm (biceps), X3-A1 ECG channel. Panel A: EEG demonstrates intermittent generalized interictal epileptic discharges, and continuous generalized slowing. Panel B: Shows low-voltage fast activity alternating with ketamine waves.

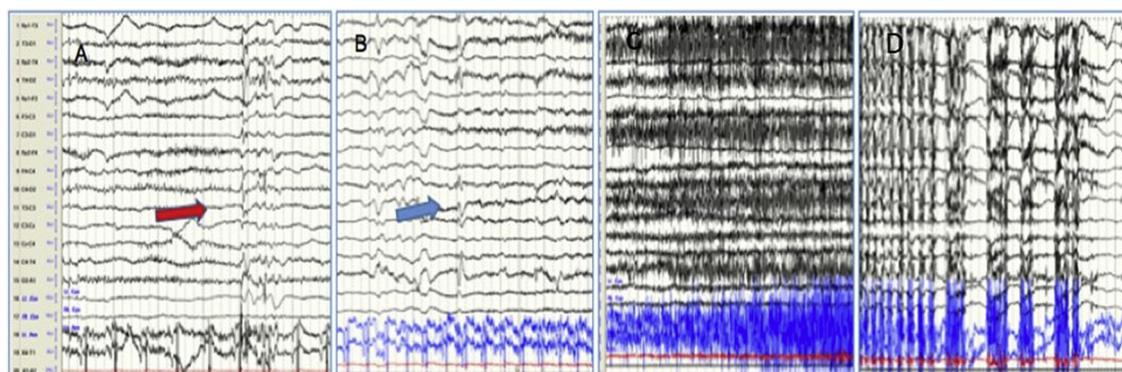


Fig. 3. Ketamine Effect on Ictal Scalp EEG.
Legend: FP frontopolar, T(emporal), O(ccipital), C(entral), Lt eye (Left epicanthus), Rt eye (Right epicanthus), Arm (biceps), X3-A1 ECG channel. Panel A: EEG demonstrates generalized spikes and polyspikes with myoclonic seizure. Panel B, C, D: Shows evolution of generalized tonic-clonic seizure. Panel B: shows onset; Panel C: Tonic phase; Panel D: Clonic phase.

generalized gamma frequency activity of 30–40 Hz frequency. After one minute, there was evidence of continuous 3–5 Hz slowing first in the posterior head regions, gradually spreading anteriorly, with gradual emergence of 4–6 Hz generalized spike-and-wave discharges (GSWD; Fig. 2A). After two minutes, fast activity became more anteriorly predominant and interrupted by 200–400 msec ketamine waves every 3–6 seconds (Fig. 2B). There was increased muscle tone for 10–15 seconds, affecting the face, arms, trunk and legs, correlated with the intervening fast activity. During the ketamine waves, there was a brief loss of tone. The ketamine waves also harbored occasional GSWDs, associated with an ocular myoclonus or generalized release myoclonus. Myoclonic seizures (Fig. 3A) and GTCS were typically recorded between 2–5 minutes post-injection (Fig. 3B–D). The GTCS lasted 20–60 seconds in duration, the shorter seizures demonstrating only brief clonic

activity. The fast activity gradually waned between 5 and 10 min post-injection, and the ketamine waves resolved. Ketamine-induced seizures could still occur in this time frame, but generally remitted before 10 min post-injection.

3.2. Intracranial-EEG

Not unexpectedly, the first EEG changes with ic-EEG preceded those noted on scalp recordings. Fig. 4 shows simultaneous sc-EEG and ic-EEG recordings in B2 at baseline (Fig. 4A). After 15 s, an increase in fronto-central beta activity was associated with more prominent spiking in the occipital regions (Fig. 4B), at times at 4–6 Hz frequency. After 30 s, similar to the scalp recording, a 40–80 Hz gamma frequency activity was noted fronto-centrally, but ic-EEG demonstrated earlier onset of



Fig. 4. Progression of Ketamine-Induced Changes on Scalp and Intracranial EEG. Legend: LGRD (left frontoparietal grid), LO (left occipital strip), RO (right occipital strip), RGRD (right frontoparietal grid), Sc-EEG: scalp EEG. Panel A: baseline recording comparing the intracranial and scalp EEG (bottom arrow). Panel B: shows occipital spikes and slowing; Panel C: dissociated EEG rhythms in the parieto-occipital regions and fronto-central regions; Panel D: Evolving burst suppression pattern in the occipital regions; Panel E: Tonic activity exhibited by baboon B2 clinically, noted with fronto-central fast activity with background suppression pattern.

occipital slowing of 3–5 Hz, which first spread centrally, then orbito-frontally, by 60 s. After one minute, the first ketamine waves emerged to disrupt the fast activity, and GSWDs were noted mainly in the periorlandic areas, as well as orbito-frontal spikes. Focal occipital seizures could occur in this time frame. By two minutes, the EEG background “dissociated” between fronto-central and parieto-occipital regions (Fig. 4C). While the fronto-central gamma activity persisted, a burst suppression pattern evolved occipitally (Fig. 4D). EEG seizures were either focal and subclinical, usually noted in the parietal or orbito-frontal regions; or generalized, often with orbitofrontal onset associated clinically with GTCS. The seizures were associated with a rhythmical 10–12 Hz discharges or PFA. The tonic activity exhibited by the baboons in association with the fronto-central gamma frequency activity emerged with the background suppression pattern (Fig. 4E). This was best observed in B2, who had simultaneous sc-EEG and ic-EEG monitoring. The occipital bursts, however, were not correlated with the ketamine waves, probably due to separate generators underlying them.

4. Discussion

In this study, we compared the effects of ketamine at low sedative doses on scalp and intracranial EEG recordings in three baboons with genetic generalized epilepsy (GGE) with a history of myoclonic and GTCS. As previously reported for sc-EEG, ketamine administered intramuscularly at doses of 5–6 mg/kg, activated generalized IEDs and elicited clinically apparent seizures in epileptic baboons (Szabó et al., 2005, 2013). While MS or GTCS were recorded most commonly, release eyelid or myoclonus was observed mainly in association with ketamine waves. Ic-EEG, however, demonstrated activation of multifocal IEDs in addition to generalized IEDs with ketamine administration, along with focal, subclinical seizures, most commonly noted in the parieto-occipital regions. GTCS were more commonly associated with orbito-frontal or fronto-central onsets. These findings are consistent with activations of focal IEDs by low-dose ketamine in people with focal epilepsy (Ferrer-Allado et al., 1973). Because of the broader cortical sampling in this animal model of GGE, we were able to document the emergence of generalized background suppression from a burst-suppression pattern beginning in the parieto-occipital regions, demonstrating vulnerability of visual cortices to ketamine.

Ketamine’s effect on EEG activity is dose-dependent (Modica et al., 1990). In people without epilepsy, sc-EEG recordings 1–2 minutes after intravenous administration of 1–3 mg/kg demonstrated a frontally predominant 30–40 Hz gamma activity, alternating with a mixture of

moderate amplitude theta and high amplitude delta activity (ketamine waves). Higher ketamine doses, exceeding 2 mg/kg, produced a generalized burst suppression pattern. Dose-dependent effects were also noted with single doses of intravenous ketamine in patients undergoing ic-EEG for temporal lobe epilepsy (Ferrer-Allado et al., 1973). At 0.5 mg/kg, only focal IEDs were noted without rendering the patient unconscious, whereas subclinical EEG and clinical seizures were induced at ketamine doses of 2 and 4 mg/kg within 2 min of its administration. The ketamine doses of intramuscular 5–6 mg/kg employed in the epileptic baboons produced similar effects but evolved more gradually over several minutes due to the drug’s slower redistribution from the muscle compartment. The physiological changes described on sc-EEG in people without epilepsy were noted on ic-EEG, but also the activation of ictal and observed in people with focal epilepsy. The more gradual absorption of ketamine after intramuscular administration also highlighted the temporal evolution of its physiological and electro-clinical effects. The physiological changes described at low intravenous doses in healthy adults, including the paroxysmal fast activity (PFA) alternating with ketamine waves, were subsequently replaced by a burst suppression pattern (Celesia et al., 1975). In this study, however, we observed an occipital to frontal propagation of ketamine-induced EEG changes. Even with respect to ictal and IEDs, initially the habitual IEDs and focal seizures were activated in the parieto-occipital regions, with subsequent evolution of atypical GTCS with a frontal EEG predominance, which were shorter in duration than spontaneous GTCS (Szabó et al., 2012a; Szabo et al., 2017). Similar dose-dependent and temporal ketamine effects were noted in baboons with experimentally-induced cerebral air embolisms, where intravenous injection of a mean ketamine dose of 9.5 mg/kg induced focal and generalized IEDs within 30–45 seconds of administration (Arfel et al., 1976). The generalized PFA was visible at 2 min, initially lasting several seconds, subsequently shortening to a second duration at 5 min. By 5 min there was a generalized BS pattern. Epileptiform activity was suppressed by an additional dose of about 4–5 mg/kg of ketamine 10 min after the first injection. However, regional (occipital to frontal) evolution was not demonstrated in this experimental model of focal epilepsy. Finally, variability of EEG patterns noted with ketamine has also been attributed to the differences in its two optical isomers (S+, R-) and their relative potency with less potent R- isomer, not capable of producing the EEG suppression to the same extent as S+ isomer (White et al., 1985; Schüttler et al., 1987).

Cerebral blood flow (CBF) measurements associated with continuous intravenous Ketamine administration further substantiate the

variable effects of ketamine in healthy human volunteers and epileptic baboons. In healthy humans, subanesthetic doses of ketamine initially infused at 0.15 mg/kg/min, during which the probands witnessed hallucinations, including sensations of floating or traveling, altered body image or perception of their surroundings, were associated with increases in CBF in several cortical and subcortical regions, except for in the occipital and posterior cingulate cortices (Långsjö et al., 2003). These effects were increased further at anesthetic doses of ketamine, which would typically be associated with a BS pattern on EEG. On the other hand, resting H₂¹⁵O-PET studies in epileptic baboons, demonstrated increased CBF occipitally, and decreased CBF frontally, compared to healthy baboons at continuous infusions at an infusion rate of 4–6 mg/kg/hr (Szabó et al., 2008). Correlation analyses with IED rate recorded by sc-EEG, which demonstrated similar CBF changes occipitally and frontally, suggested that ketamine administered at steady, low infusion rate caused continuous activation of generalized IEDs involving parieto-occipital cortices, and not their deactivation, which would have suggested underlying background suppression.

As mentioned above, ketamine is thought to lower IED and seizure thresholds in people predisposed to epilepsy, due to a transient increase in glutamate secretion or of glutamatergic neurotransmission, and possibly a sustained increase via AMPA receptors (Modica et al., 1990; Moghaddam et al., 1997). What is not clear is why the visual cortices are affected initially by ketamine administered intramuscularly, and why are seizures first provoked in the visual cortices, then later in the frontal lobes. One explanation may be that in the baboon, NMDARs are decreased in all layers of primary visual cortices compared to the frontal lobes (Geddes et al., 1989). The relative reduction of NMDARs in the visual cortices will render them more susceptible to lower ketamine concentrations early on, both with respect to the initial proconvulsant and the delayed anesthetic effects. Due to the higher concentration of NMDARs, increasing levels of ketamine will eventually affect the frontal lobes in a similar fashion. Hence, by the time seizures are triggered in the frontal lobes, the visual cortices are already suppressed. This difference in regional effects may not be as apparent with intravenous ketamine administration or anticonvulsant doses of ketamine. It would be of interest to evaluate ketamine's electroclinical effects in epileptic baboons pretreated with perampanel, an AMPA receptor antagonist and/or felbamate, an NMDA receptor modulator, with respect to the severity of increased seizure susceptibility and the duration of decreased seizure thresholds after ketamine administration.

The shortfalls of this study include retrospective analysis of a small sample size, the short duration of the sc- and ic-EEG studies, and the reliance on mainly the second ketamine injection for analysis when the baboons were still mildly affected by the first dose. The time frame of monitoring was short with lack of dose variability. We have not recorded the later period of EEG during which ketamine may have raised the seizure thresholds. Nonetheless, our results were similar to those described by the study performed in baboons with acute embolic strokes, with respect to both the physiological changes and the exacerbation of IEDs and seizures (Arfel et al., 1976).

5. Conclusions

This study highlights the proconvulsant nature of low-dose ketamine and provides insight into its inter-regional and progressive EEG effects. The first EEG changes on ic-EEG were noted in the occipital lobes, which appear to be most vulnerable to ketamine's proconvulsant glutamatergic effect. We speculate that the difference of cortical NMDAR concentrations in the primary visual cortices and frontal lobes underlies the variable, dose-dependent effect of ketamine, both with respect to its proconvulsant and anesthetic effects.

Conflict of interest

Authors do not have any conflict of interest.

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