Effects of Ketamine on Basal Gamma Band Oscillation and Sensory Gating in Prefrontal Cortex of Awake Rats

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Abstract Gamma band oscillation (GBO) and sensory gating (SG) are associated with many cognitive functions. Ketamine induces deficits of GBO and SG in the prefrontal cortex (PFC). However, the time-courses of the effects of different doses of ketamine on GBO power and SG are poorly understood. Studies have indicated that GBO power and SG have a common substrate for their generation and abnormalities. In this study, we found that (1) ketamine administration increased GBO power in the PFC in rats differently in the low- and high-dose groups; (2) auditory SG was significantly lower than baseline in the 30 mg/kg and 60 mg/kg groups, but not in the 15 mg/kg and 120 mg/kg groups; and (3) changes in SG and basal GBO power were significantly correlated in awake rats. These results indicate a relationship between mechanisms underlying auditory SG and GBO power.

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Introduction

Gamma band oscillations (GBOs) are 30 Hz–90 Hz waveforms in the EEG [1] and are associated with many cognitive functions, such as short-term memory [2], working memory [3], selective attention [4] and cognitive control [5, 6]. In recent years, abnormal GBO power has been considered to underlie cognitive deficits and has attracted attention as a translational biomarker for schizophrenia [7]. Sensory gating (SG) has been conceptualized as a continuously active process that contributes to an individual's ability to modulate a continuous stream of sensory and cognitive information [8]. This process allows the central nervous system to selectively attend to important stimuli while ignoring redundant, repetitive, and trivial stimuli [9]. Auditory SG can be tested using sound stimuli in a conditioning-testing paradigm and has been found to be defective in schizophrenic patients and animal models [10, 11].

Ketamine is a non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonist and has various effects in the nervous system depending on the dose. For example, ketamine is an efficient drug for the treatment of depression in a single sub-anesthetic dose (0.5 mg/kg, intravenous) [12–14], can be used in a sub-anesthetic dose (~10 mg/kg, intraperitoneal or subcutaneous) to establish schizophrenia models that show positive, negative, and cognitive symptoms similar to schizophrenic patients [15], and is also used at a high dose as an anesthetic for laboratory animals and humans [16, 17].

Ketamine induces abnormal GBO power in the prefrontal cortex (PFC) of humans and rats [18–20]. It has been reported that basal GBO power shows an inverted U-shaped dose-response curve in the first 30 min after administration of 2.5 mg/kg–30 mg/kg ketamine [21]. It is also known that deficits of SG can be induced in the rat PFC by ketamine [15, 22]. However, studies on the time-course of the effects of different doses of ketamine on GBO power and SG are rare.

As both GBO power and SG are damaged in the PFC of schizophrenic patients and impaired by NMDAR antagonists, we may ask whether these changes are correlated. Although the detailed mechanisms of basal GBO abnormality remain unclear, they may have a close relationship with the function of inhibitory interneurons [23, 24], especially a disturbance of parvalbumin basket cells (PVBCs) [24, 25], gamma-aminobutyric acid (GABA) interneurons that modulate the activity and synchrony of pyramidal neurons [26, 27]. Auditory SG involves multiple neurotransmitter systems and recurrent inhibitory and excitatory circuits with endogenous and exogenous inputs to the PFC [28–30]. Studies suggest that the conditioning stimulus (first sound) activates both inhibitory and excitatory circuits and that the inhibitory activity acts as a comparator to reduce the excitatory response to an identical test stimulus (second sound) presented while the inhibitory circuits are still active [29, 31, 32]. Recently, a study reported that dysfunction of PVBCs leads to a deficit of SG [33]. These studies indicate that GBO power and SG may have a common substrate for their generation and abnormalities. If this is true, changes of GBO power and SG would be correlated.

In this study, the time courses of the effects of different doses of ketamine on GBO power and SG in the PFC were explored, and possible correlations between changes of SG and GBO power in the PFC were tested.

Materials and Methods

Animals

Thirty-two adult male Sprague-Dawley rats (Animal House Center, Kunming Medical College, China) (8–10 weeks old, 250 g–350 g) were used in the experiments. The rats were housed under standard conditions and cared for under the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80–23, revised 1996). Experiments and all related protocols were approved by the Ethics Committee of the Kunming Institute of Zoology (AAALAC accredited), Chinese Academy of Sciences.

Surgery

EEG electrodes were implanted according to the method described in our previous work [34]. In brief, the rats were anesthetized with pentobarbital sodium (50 mg/kg, intraperitoneal injection; Hengrui Medical Co., Jiangsu, China) and deep anesthesia was monitored by the toe-pinch reflex test. EEG was recorded through 3 screw electrodes (1.2 mm diameter) inserted into holes drilled in the skull according to a rat brain atlas (Paxinos and Watson, 2007). One electrode was placed over the PFC (A–P, –4.5 mm; M–L, 1.5 mm) as the recording electrode, one over the olfactory bulb as the reference electrode, and the third over the cerebellum as the ground electrode. The implanted rats were given penicillin for two days (0.2 million U/day) and allowed to recover for 2 weeks.

EEG Recording

EEGs were recorded during the light phase of the light/dark cycle and the animals were unrestrained. The procedures are described in detail in our previous paper [34]. In short, after recovery from surgery and 2 days of adaptation to the sound-proof box, recording was performed on day 3 from 08:30 to 14:00. The recording included 30 min of baseline recording and 5 h of recording after drug administration. The EEG signals were amplified and digitized using a Symtop amplifier (UEA-FZ 41, Symtop Instrument Co., Ltd, Beijing, China). The signals were sampled at 1000 Hz and band-filtered from 0.1 Hz to 120 Hz with an analog notch filter at 50 Hz. Rat behavior was monitored by a video camera (HD91, GUCEE, Shenzhen, China), which was positioned approximately 1 m above the rat's cage.

Stimulus Paradigm and Drug Administration

Sound stimuli (5000 Hz, 10 ms duration) of the conditioning-testing paradigm were produced by Psychtoolbox-3 in Matlab (MathWorks, Natick, MA). The conditioning (first sound) and testing sounds (second sound) were delivered at 80 dB (SPL) with a 500-ms inter-stimulus interval and with a 5 s–10 s random inter-trial interval to prevent habituation. The stimuli were presented through a loudspeaker (E3010, Vigoo, Shenzhen, China) ~35 cm directly above the floor of the rat cage.

Ketamine hydrochloride (0.1 g/2 mL, Shanghai Medical Co., Shanghai, China) was dissolved in sterile saline. The animals were divided into 5 groups and given five doses of ketamine (0 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, and 120 mg/kg; $n = 5, 6, 8, 8, \text{ and } 5$, respectively). Ketamine was administered intraperitoneally in a volume of 1 mL per rat.

Data Analysis

EEG data were analyzed off-line in Matlab. The GBO was calculated as follows: (1) data were band-filtered from 0.5 Hz to 90 Hz in the EEGLab toolbox and artifacts were rejected by visual examination; (2) the fast Fourier transform was calculated in a sliding window (10 s) to provide a power spectrum over time (spectrogram) using Chronux (<http://chronux.org>). The spectrogram was then averaged in 2-min bins to develop a heatmap of the spectrogram. For time-course analysis, GBO (30 Hz–90 Hz), delta band (1 Hz–4 Hz), theta band (4 Hz–8 Hz), alpha band (8 Hz–12 Hz), and beta band (12 Hz–30 Hz) power were extracted from the power spectrum analysis and normalized to the 30 min of baseline recording. The power curve for each rat was smoothed by averaging 5 points (10 min) in the original data.

The maximum values (peaks) of GBO power, the latencies of the peaks and the 1/2 peaks (in the descending phase) during the 300-min period after drug administration were obtained from the smoothed curves.

SG was tested using auditory evoked potentials (AEPs) and a single AEP waveform was computed by averaging 150 trials (~30 min). Analysis was as in our previous paper [34]. In brief, the SG was quantified as the ratio of the amplitudes of the test sound (TAMP) and the conditioning sound (CAMP). A TAMP/CAMP (T/C) ratio close to 1 indicated no or low SG, while a T/C ratio close to 0 indicated robust suppression.

Correlations between changes in GBO power and SG in the PFC after different doses of ketamine during the waking state were calculated, since the auditory SG is markedly affected by the state of vigilance [34]. Auditory SG in the frontal cortex is lower during non-rapid eye movement (NREM) sleep than in the waking state in rats. The criteria for differentiation of vigilance states by EEG signals and behavioral videos were based on previously published methodology [34, 35]. The latency to NREM sleep was defined as the time from drug administration to the beginning of NREM sleep.

Statistical Analysis

All data were processed with the SPSS software package (version 21; SPSS, Chicago, IL). The effects of ketamine dose on the value of the GBO power peak, and the latencies of the peak and 1/2 peak, were analyzed with the Bonferroni *post-hoc* test to assess the differences between groups.

One-way repeated-measures ANOVA was used to examine the time-course of SG changes during the time between drug administration and onset of NREM sleep from the 30-min baseline recording, followed by the

least significant difference (LSD) correction *post-hoc* test to determine which time bins differed from baseline.

The correlation between changes of GBO power and SG (normalized to 30-min baseline recordings) in the PFC of awake rats after administration of different doses of ketamine was determined by linear regression analysis. A statistically significant standard was set at $P < 0.05$ with a 95% confidence interval.

Results

Time-Course of Effects of Different Doses of Ketamine on GBO Power in the Rat PFC

The GBO power (30 Hz–90 Hz) was increased after 60 mg/kg ketamine compared to baseline (Fig. 1A). GBO power was higher during the 300-min period after ketamine administration at each of the doses than in the control group (Fig. 1B), but the changes in the power of the other bands (delta, theta, alpha and beta) were much less sensitive to the dose of ketamine (Fig. S1). Ketamine dose had significant effects on the time-course of GBO power, including the peak and 1/2 peak latencies (in the descending phase) (both $P < 0.001$, one-way ANOVA). *Post-hoc* tests using Bonferroni correction showed that there was no difference in the latency of the GBO power peak or 1/2 peak between the 15 and 30 mg/kg groups (16.67 ± 2.99 min *versus* 19.75 ± 5.56 min for peak and 95.67 ± 8.88 min *versus* 97.25 ± 8.07 min for 1/2 peak). It took longer time in the 60 mg/kg group than in the 15 mg/kg and 30 mg/kg groups to reach a peak (55.01 ± 7.80 min) and to decrease to the 1/2 peak value (157.25 ± 9.85 min) (all $P < 0.05$). The 120 mg/kg group took the most time among all groups to reach a peak (92.80 ± 14.22 min) and decrease to 1/2 peak value (247.20 ± 29.81 min) (all $P < 0.01$) (Fig. 1C).

The ketamine dose also affected the value of GBO peak power ($P < 0.001$, one-way ANOVA). The GBO peak power was higher in the 30 mg/kg group than in the control group ($P = 0.006$, *post-hoc* Bonferroni test), higher in the 60 mg/kg group than in the control and 15 mg/kg groups ($P < 0.001$ and $P = 0.032$, respectively, *post-hoc* Bonferroni test), and higher in the 120 mg/kg group than in the control, 15, and 30 mg/kg groups ($P < 0.001$, 0.001 and $P = 0.006$, respectively, *post-hoc* Bonferroni test) (Fig. 1D).

These results suggested that the values of GBO power increased rapidly to a peak and decreased slowly after ketamine administration in the low-dose groups. However, the values of GBO power both increased and decreased slowly in the high-dose groups. So ketamine administration

Fig. 1 Effects of different doses of ketamine (0 mg/kg, 15 mg/kg, 30 mg/kg, 60 mg/kg, and 120 mg/kg) on GBO power in rat PFC. **A** Heatmap of EEG power in the 20 Hz–90 Hz range in a rat. The time course includes a 30-min baseline and 300 min of recording after administration of 60 mg/kg ketamine. **B** Upper panel: changes of GBO power in the PFC during 30-min baseline and 300 min of recording after ketamine administration at the indicated concentrations. The data were averaged into 2-min bins and are expressed as mean $\pm$ SEM. Each data point was normalized to the average of the 30-min baseline. Lower panel: smoothed curves of GBO power from

data in the upper panel. Arrows at 0 indicate the time of drug administration. **C** Latencies of GBO power to reach peak and then to decrease to 1/2 peak (in the descending phase) values during the 300 min after ketamine administration. **D** Peak values of GBO power during the 300 min after ketamine administration. Values were from the smoothed curves and expressed as mean $\pm$ SEM. * P < 0.05 compared with control group (one-way ANOVA using Bonferroni correction); # P < 0.05 compared with 15 mg/kg group; & P < 0.05 compared with 30 mg/kg group; ^ P < 0.05 compared with 60 mg/kg group.

increased GBO power in different ways in the low- and high-dose groups.

Time-Course of Effects of Different Doses of Ketamine on SG in the PFC of Awake Rats

In a previous study, we found that auditory SG is lower in the frontal cortex during NREM sleep than in the waking state in rats [34] and the waveforms of the AEPs in response to sound stimuli given in the conditioning-testing paradigm during waking and NREM sleep were quite different (Fig. 2A). We carried out this study in daytime, when rats spend most of the time sleeping. We analyzed the auditory SG during waking but not sleep to exclude the effects of state. The latencies to NREM sleep in the five groups (0, 15, 30, 60, and 120 mg/kg) were 42 ± 5.03 min, 55 ± 5.02 min, 155 ± 18.03 min, 200 ± 10.24 min, and 260 ± 26.17 min, respectively (Fig. 2B).

Auditory SG decreased to different levels in the PFC after administration of different doses of ketamine in awake rats (Fig. 2C). The T/C values increased and gradually returned to normal with time. One-way repeated-measures ANOVA of the five groups of data showed that the auditory SG was lower (T/C values

increased) than baseline after 30 and 60 mg/kg ketamine ($P = 0.02$ and 0.05) at 120 min and 180 min, respectively. *Post-hoc* LSD correction indicated that auditory SG was lower than baseline at 0–30 min after 30 mg/kg ketamine ($P = 0.003$) and at 0–30 min, 30–60 min, and 60–90 min after 60 mg/kg ketamine ($P = 0.008$, 0.025 and 0.045 , respectively).

Changes in Auditory SG are Associated with GBO Power in the PFC of Awake Rats after Ketamine Administration

Correlations between the changes of GBO and SG in the PFC after different doses of ketamine were calculated during the waking state. Given that the relationship between GBO and SG depended on changes induced by ketamine, we restricted our analysis of the correlations to the three highest ketamine doses and found positive linear correlations between the changes of the values of T/C (normalized to 30-min baseline) and the GBO power after 30 mg/kg, 60 mg/kg, and 120 mg/kg ketamine ($R^2 = 0.851$, 0.834 , and 0.742 , respectively; Fig. 2D).

Our results showed that auditory SG decreased with the increase of GBO power and returned to normal with a

Fig. 2 Effects of different doses of ketamine on auditory SG and GBO power in the rat PFC. **A** Representative waveforms of auditory evoked potentials (AEPs) in response to sound stimuli given in the conditioning-testing paradigm during waking and NREM sleep. Blue, conditioning sound; red, test sound; black line, start of sound stimuli. **B** Latencies to NREM sleep after ketamine administration in the five groups. Data are expressed as mean $\pm$ SEM. **C** Changes of auditory

SG (compiled in 30-min bins) from the 30-min baseline until the rats entered NREM sleep after different doses of ketamine. Data are expressed as mean $\pm$ SEM; $*P < 0.05$ (one-way repeated-measures ANOVA with LSD correction). **D** Correlations between the T/C ratios (normalized to 30-min baseline) and the GBO power after the three highest levels of ketamine (30 mg/kg, 60 mg/kg, and 120 mg/kg, $R^2 = 0.851$, 0.834 , and 0.742 , respectively).

decrease of GBO power to the normal range after ketamine administration. These results suggest a relationship between the mechanisms underlying auditory SG and GBO power affected by ketamine in the PFC in awake rats.

Discussion

In this study, we found that 15 mg/kg, 30 mg/kg, 60 mg/kg, and 120 mg/kg ketamine increased GBO power to different levels, but not that of other bands (delta, theta, alpha and beta) in the rat PFC. Many studies have shown that sub-anesthetic doses of ketamine increase GBO power in the medial PFC of freely-moving rats [36, 37]. Furthermore, our studies have demonstrated that the ketamine dose has effects on the time-course of GBO power and SG in the PFC of rats; the values of GBO power increased rapidly to a peak and decreased slowly after ketamine administration in the low-dose groups. However, the values of GBO power both increased and decreased slowly in the high-dose groups. So ketamine administration increased GBO

power differently in the low- and high-dose groups. We know that ketamine has various applications in the nervous system according to the dose, but the detailed time-courses of different doses for GBO power are poorly understood. Our results will be helpful for understanding the dynamic effects of different doses of ketamine on brain function.

Our results showed that it took longer for the high-dose groups to reach the peak of GBO power than the low-dose groups after ketamine administration, consistent with previous work. Intraperitoneal plasma concentrations of ketamine reach a peak within 5 min–15 min [38] due to both its water and lipid solubility [39]; this may explain the latencies of the GBO power peaks in the low-dose groups (15 mg/kg and 30 mg/kg). Many studies have shown that the half-life of ketamine is ~ 2 h in 8–12 week-old rats [39, 40], so the longer latencies of the GBO power peak in the 60 mg/kg and 120 mg/kg group may be related to the metabolic characteristics of ketamine.

Much work has shown that the generation of GBO is closely associated with the activity of PVBCs [25, 41, 42]. The Pyramidal Interneuron Network Gamma model

provides a reasonable explanation of how inhibitory PVBCs are related to the production of GBO. In this model, interneurons are driven by phasic (synaptic) excitatory glutamate-mediated currents arriving from pyramidal cells, which are rhythmically synchronized by feedback inhibition [25]. Many studies have shown that NMDARs preferentially drive the activity of inhibitory cortical interneurons and suggest that NMDAR inhibition causes an increase in GBO power *via* the disinhibition of pyramidal neurons [26, 27]. These reports and our results suggest that ketamine binds to NMDARs on inhibitory interneurons and causes an increase in GBO power at low-medium doses. With dose increments, there seems to be a ‘sensitive’ dose at which ketamine saturates the NMDARs on inhibitory interneurons and increases GBO power in the shortest time frame. However, with the addition of more concentrated ketamine and saturation of the NMDARs on inhibitory interneurons, the excess antagonist then binds NMDARs on pyramidal neurons, decreasing the GBO power by inhibiting pyramidal neurons. With the metabolism of ketamine, it is possible that the plasma concentration decreases to the ‘sensitive’ dose and the GBO power then increases to the maximum. This interpretation may explain the longer latencies to reach GBO peak power in the 60 mg/kg and 120 mg/kg groups (Fig. 1B).

We found that auditory SG was significantly lower than baseline 30 and 120 min after 30 and 60 mg/kg ketamine administration, but no significant changes were found in the 15 mg/kg and 120 mg/kg groups. In a previous study, we found that the state of vigilance affects the auditory SG, which decreases significantly from waking to NREM sleep [34]. So, in this study, we just analyzed the changes of auditory SG in the waking state. It has been reported that SG is impaired by a sufficient amount of ketamine [43], but we found that 15 mg/kg ketamine did not cause significant decreases in the auditory SG. The rats were anesthetized after 120 mg/kg ketamine administration, the reaction of the central nervous system to external stimuli was repressed, CAMP and TAMP were very small, and the ‘T/C’ ratio was susceptible to random factors, so its trend was unstable, resulting in non-significant changes in the 120 mg/kg group (Fig. 2C). In our data, the mean T/C ratio at 30 min was higher than baseline in the control group, which may have been induced by the drowsy state of rats, for our experiments were carried out in daytime.

Both the decrease of SG and increase of basal GBO power might be related to the hyperactivity of pyramidal neurons and hypoactivity of interneurons in the PFC. To determine whether the variable trends of SG and GBO in the PFC are correlated after ketamine administration, we evaluated the results with linear regression analysis of the three higher doses of ketamine. The analysis revealed that the changes in T/C ratio and basal GBO power had positive

linear correlations in the 30 mg/kg, 60 mg/kg, and 120 mg/kg ketamine groups.

The medial PFC plays a critical role in the generation of auditory SG [9, 44]. Previous studies using ensemble recordings in freely-moving rats have shown that NMDA antagonist treatment potentiates the firing rate of most PFC neurons, but less organized bursting activity is also found [45]. This indicates that NMDA antagonists increase disorganized spike activity, which enhances cortical noise and hinders the transmission of information [46]. Moreover, it indicated that the decrease in burst activity reduces the transmission efficacy of cortical neurons. This may explain why auditory SG decreased (T/C increased) and GBO power increased in the PFC of rats given an intermediate dose of ketamine (30 mg/kg or 60 mg/kg) in our study.

Some aspects of this study could be improved. First, local field potentials may be better than the EEG for defining the relationship between basal GBO power and local SG in the PFC. Second, the plasma concentration of ketamine was not continuously monitored after administration. Third, more groups with smaller increments of dosage than those currently used would benefit the study by verifying the effects of ketamine dose on the basal GBO power and SG.

In conclusion, we have demonstrated the time-course of the effects of different doses of ketamine on GBO power and SG in the rat PFC. We found that ketamine increased GBO power in different ways. The results will be helpful to understand the dynamic effects of different doses of ketamine on brain function. Furthermore, we also found a significant correlation between changes of basal GBO power and SG in the PFC after administration of 30 mg/kg, 60 mg/kg, and 120 mg/kg ketamine. The basal GBO power and SG have been reported to be aberrant in schizophrenic patients and animal models, so our results suggest that common mechanisms underlie the roles of basal GBO power and SG dysfunction in schizophrenia.

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