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Ketamine, an NMDA-antagonist, increases the oscillatory frequencies of α-peaks on the electroencephalographic power spectrum

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Background: Ketamine, an *N*-methyl-D-aspartate (NMDA) antagonist, is known to activate the electroencephalogram (EEG), despite its sedative effects. Spindle oscillations are known to be related to the sedative actions of the reticular thalamic nucleus with links to thalamocortical neurons. This study was designed to examine the effect of ketamine on the spindle oscillations to understand the simultaneous sedative effect and EEG activation that occurs with ketamine, by comparing the EEG in emergence.

Methods: Anesthesia was induced with propofol using a target-controlled infusion (TCI) system (3.5 μg/ml). Seventeen patients, scheduled for non-cranial surgery under general anesthesia combined with epidural anesthesia, were randomly divided into two groups: (i) anesthesia was maintained with TCI-propofol alone ($n = 8$) and (ii) anesthesia was maintained with TCI-propofol and intravenously administered ketamine ($n = 9$). The EEG was continuously monitored and EEG indices and power spectra were determined.

Results: Propofol alone caused the α-peaks of the power spectra to occur at an average frequency of 10.4 ± 0.9 Hz; the addition of ketamine shifted the peaks to higher frequencies of 15.1 ± 1.4 Hz ($P < 0.05$). On the other hand, when the EEG was activated by discontinuation of propofol, the corresponding α-peaks disappeared.

Conclusions: Ketamine increased the frequencies of α-spindle waves induced by propofol, but did not block their formations. The phenomena have the possibility to underlie the cooperative effect between propofol and ketamine concerning sedation and anesthesia.

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Key words: Spectral analysis; *N*-methyl-D-aspartate; spindle wave; reticular thalamic nucleus; thalamocortical system.

The sedative effects of general anesthetics are believed to be mediated via two different pathways: the cortical pathway, and the subcortical thalamic relay and reticular neuron pathway (1–4). There is now broad agreement that γ-aminobutyric acid ($GABA_A$) and *N*-methyl-D-aspartate (NMDA) receptors are important sites of effects of general anesthetics, and that anesthetic-induced synchronization and depression of neural activity in the cerebral cortex is linked to subcortical arousal systems, reflecting a complex interplay of thalamic neurons (1–4). The addition of ketamine, an antagonist of the NMDA subtype of excitatory glutamate receptors, to propofol, an agonist of $GABA_A$ receptors, is known to reduce the dose of propofol required to achieve hypnosis, suggesting an additive interaction between propofol and ketamine. However, concurrent administration of propofol and ketamine does not lead to proportionate suppression of electroencephalogram (EEG) activity (5). Ketamine is reported to independently increase β activity (6). Another study found that low-dose ketamine significantly decreased the absolute amplitude of slow activity, and markedly reduced the α amplitude without the appearance of θ activity (7). Thus, many studies have suggested that ketamine increases EEG activity (8–10). Ketamine, however, being an antagonist of excitatory NMDA neurons, competes with excitatory transmitters at NMDA-receptors at the cortical level, as described previously (3), and hence, is expected to suppress neural activity and cause slowing of the EEG. The gap between theoretical intuition and actual observation seems to arise from the fundamentally complex mechanisms of

mediation of the effects of anesthetics, which include dual cortical and subcortical effects, and which may underlie the difficulty in identifying universal EEG markers for hypnosis.

During propofol anesthesia, spindle-like oscillatory rhythms at around 10 Hz become dominant on the power spectrum of the EEG. Propofol has been reported to induce strong frontal-central rhythms in the α-range (11–13). The rhythms are analogous to 'the classic α rhythm' which appears during wakefulness particularly over the occipital cortex, mainly distributed along cortico-cortico pathways. However, the quantitative characteristics of the underlying oscillatory rhythms are different from the classic α waves. It rather resembles to spindle-waves of sleep and barbiturate, which generated in the thalamus and exclusively distributed to neocortex along thalamocortical (TC) axons (11–13). The inhibitory GABA-containing neurons in the reticular thalamic nucleus (RE) are mainly responsible for the genesis of these spindle oscillations in the thalamus (1, 3, 13–15), with linking to a synaptic network containing TC and cortical pyramidal neurons. Because spindles are characterized by prolonged inhibitory post-synaptic potentials (IPSPs) in TC cells, the oscillations are effective in eliminating the synaptic transmissions of incoming volleys, and thus produce unresponsiveness and loss of consciousness. Targeting of spindle waves may therefore be useful in examining the sedative effect of anesthetics.

While non-linear thalamic contributions to the spindle activity are reflected only by phase analysis of wave synchronization, the synchronous neural oscillations of the spindle waves, with increases or decreases in amplitude as a result of the number of active neurons firing in synchrony, can be detected by synchronous peaks at α frequency area on the power spectral analysis (15). Precise examination of the effects of anesthetics on the spindle peaks of the power spectra, as well as phase analysis, may therefore be necessary to help determine the sedative mechanism of anesthetics.

Although there have already been some reports on the combined effects of ketamine and a $GABA_A$ agonist on the raw EEG and more complex EEG-derived indices, many of them missed the detail reports about α spindle waves. In the present study, we examined the effects of an NMDA-antagonist on α-peaks of the EEG power spectra with concurrent administration of a $GABA_A$-agonist using TCI technology, and thus were able to determine the backgrounds of the sedative interaction of an NMDA-antagonist and a $GABA_A$-agonist through the spindle genesis. We are interested in whether ketamine blocks the formations of α spindle waves.

Materials and methods

Patients

After obtaining approval from the institutional ethics committee and written informed consent from all patients included in the study, 17 patients [between 20 and 60 years of age, American Society of Anesthesiology (ASS) grade I or II] scheduled for elective abdominal surgery under general anesthesia combined with epidural anesthesia were recruited. None of the patients had any neurological or psychiatric disease, nor had they been treated with any drugs known to modulate effects of anesthetic or analgesic agents. Patients were randomly divided into two groups: (i) anesthesia was maintained with propofol alone (Group P, $n = 8$) and (ii) anesthesia was maintained with propofol, and with ketamine (1 mg/kg) intravenously injected in addition to propofol (Group PK, $n = 9$).

Anesthesia protocols

Figure 1 shows the protocol, which was followed in all patients in both groups. Patients received no premedication except 0.5 mg of atropine administered intramuscularly 30 min before the induction of anesthesia. Upon arrival in the operating theatre, an epidural catheter was inserted into the Th11–12 interspace and positioned 4 cm within the epidural space, and the effect of epidural analgesia was confirmed using 1% lidocaine (initial dose: 70–100 mg). EEG monitoring with an ASPECT A-2000 bispectral index (BIS) monitor (version 3.3; Aspect Medical Systems, Natick, MA) was started, and EEG data were continuously collected. Anesthesia was induced with propofol, using a computer-assisted target controlled infusion (TCI) system (TE-371; Terumo, Tokyo, Japan) (16). After the TCI system achieved the target effect site concentration of propofol (3.5 μg/ml) on the display, tracheal intubation, facilitated by 0.15 mg/kg vecuronium, was performed. Anesthesia was maintained with TCI-propofol (3.5 μg/ml) and 30% oxygen in air, and 0.08 mg/kg/h vecuronium was administered to obtain sufficient muscle relaxation during surgery. Mechanical ventilation was adjusted to keep the end-expired concentration of carbon dioxide between 35 and 40 mmHg, and 0.12 ml/kg of 0.375% ropivacaine was injected into the epidural space. Baseline analysis was performed in both groups 20 min after epidural injection of ropivacaine. The same dose of

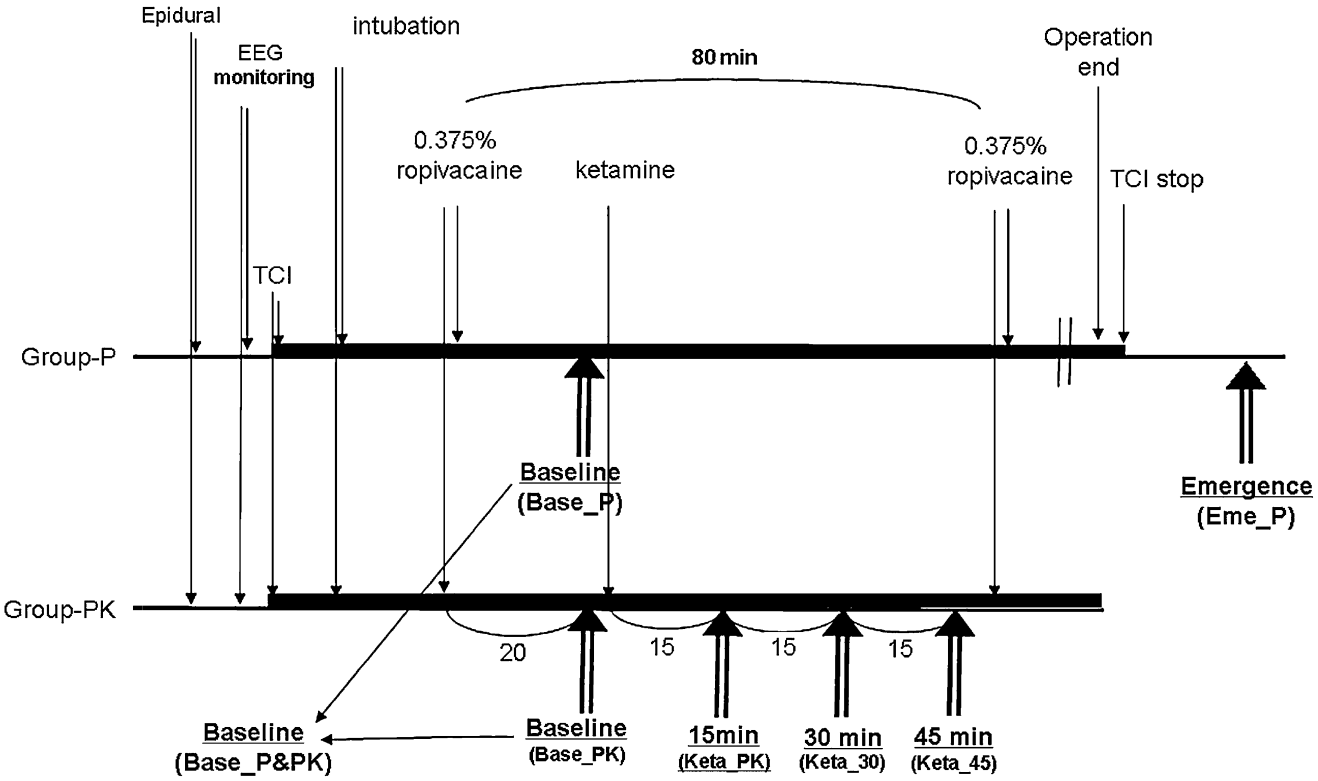

Fig. 1. The protocol followed in all patients of both groups. Measurements of electroencephalogram (EEG) indices and power spectral analysis were performed at two time points, baseline (Base_P) and emergence (Eme_P), in Group P, and at two time points, baseline (Base_PK) and 15 min after ketamine injection (Keta_PK), in Group PK. Change in spindle peaks was examined using spectral analysis at four time points (Baseline: Base_PK, 15 min: Keta_PK, 30 min, 45 min after ketamine injection) in Group PK.

ropivacaine was added every 80 min. Two cases in which epidural analgesia and/or the target concentration of propofol were insufficient to obtain clinically satisfactory anesthesia were excluded from the study.

In Group PK, immediately after EEG baseline measurements (Base_PK), patients received a ketamine bolus (1 mg/kg) administered intravenously. EEG analysis was performed at 15, 30, and 45 min after ketamine injection (Keta_PK, Keta_30, Keta_45). We examined ketamine-induced activation of the EEG under propofol-TCI (Keta_PK) by comparing it with baseline EEG within Group P (Base_PK). In Group P, propofol-TCI was discontinued when the surgery was finished. The awakening process after interruption of the administration of propofol (emergence, Eme_P) was examined when the target effect site concentration was reduced to zero on the display, by comparison with the baseline within Group P. Finally, we compared ketamine-induced activation of the EEG (Keta_PK, Group PK) with the process of emergence induced by discontinuation of propofol (Eme_P, Group P).

Data acquisition and analysis

An ASPECT A-2000 monitor was used to collect EEG data. A BIS sensor (EEG-electrodes, Aspect medical systems), consisting of three electrodes, was applied to the forehead, with the recording lead at Fp1-A1 and the reference at Fpz. The A-2000 checked electrode impedance every 10 min, and the impedance was maintained at 5 kΩ or less throughout the study. All binary data packets, containing raw EEG wave signals (converted from analog to digital in 128 Hz frequency) as well as BIS and other processed parameters, were recorded via an RS232 interface on a personal computer (CF02; Panasonic, Osaka, Japan) using the Bispectrum Analyzer BIS A-2000 version (BSA Ver3.22B2) developed with C^{++} Builder Ver5.0 (Borland, Tokyo, Japan) by us (17–19). We used artifact flags obtained from the A-2000 BIS monitor, and excluded epochs containing artifacts. Furthermore, we rejected epochs containing signals over 200 μV in amplitude, for the removal of the EEG packets including noise induced by electrocautery. We calculated the signal quality index (SQI) as the ratio of the number of epochs used for calculation to

the total number of epochs, and adopted only the values obtained from periods with SQI > 0.8. The low-pass filter was set at 50Hz, and we used subtraction of the moving average to cut signals below 0.5 Hz. BIS values were calculated by the A-2000 from the preceding 1-min period of EEG recording (more precisely, 61.5 s), and were extracted to a personal computer directly from the A-2000. EEG parameter, spectral edge frequency (SEF95), was calculated from the averaged power spectrum over 1 min by us, which were made from 2-s epochs (overlapped by 75%) after applying Blackman's window (15, 20). AMP, defined as the voltage halfway between the positive peak and negative peak, was calculated from waves with amplitudes of more than 5 μV, and averaged over 1 min. For detailed analysis at the indicated points in both groups, the averaged power spectra thus calculated were recorded from 0.5Hz to 47.0Hz at 0.5-Hz intervals, and were converted to a normalized form, i.e. the ratio of the individual power to total power within the frequency range from 0.5Hz to 47.0Hz at 0.5-Hz intervals. Normalized power spectra were then divided into six frequency ranges: δ-area (0.5–3.5 Hz), θ-area (4–7.5 Hz), α-area (8–12.5 Hz), β1-area (13–17.5 Hz), β2-area (18–30Hz) and γ-area (30.5–47 Hz). Then, the sum of normalized power in each frequency range was calculated.

Statistical analysis

For the comparison of the EEG parameters (Tables 2 and 3), Mann–Whitney's *U*-test was used between Groups PK and P, and Wilcoxon's signed-ranks test was used within the same group. Demographic data between Groups P and PK were analysed using the unpaired *t*-test (Welch's *t*-test). The hemodynamic parameters over time, and the shifts of mean spindle peaks before and after injections of ketamine (Fig. 5), within the same groups, were analysed using the paired *t*-test, because the distributions were regarded as the normality assumption using the Shapiro–Wilk normality test. Findings of $P < 0.05$ were considered significant. The statistical comparisons were analysed using Statview version II (SAS, Cary, NC).

Results

The background factors for each group are shown in Table 1. There were no significant differences between the groups in terms of patient age, weight or duration of surgery (Table 1). The hemodynamic parameters mean arterial pressure (MAP) and heart rate (HR) before and after ketamine injection in Group PK were 91.4 ± 15.9, 90.3 ± 19.3, 86.0 ± 18.3, 88.0 ± 16.2 (mmHg) and 62.7 ± 8.4, 60.9 ± 9.2, 61.2 ± 8.6, 63.2 ± 10.4 (bpm), respectively (baseline, 15 min, 30 min, and 45 min after injection of ketamine). No significant circulatory changes were found between the time points of data collection.

Table 1

Demographic data in each group.

Group	Age (years)	Weight (kg)	Gender (M/F)	Duration of surgery (min)
Group P	51.4 ± 16.2	65.8 ± 16.4	6/2	271.9 ± 209.9
Group PK	53.6 ± 12.8	61.5 ± 12.1	4/5	234.4 ± 108.1

Table 2 shows the EEG variables SEF95, BIS and AMP recorded under the following conditions: (i) propofol alone (Base_P & PK, Base_PK, Base_P), (ii) 15 min after ketamine injection (Keta_PK, $n = 9$) and (iii) the process of emergence after discontinuation of administration of propofol (Eme_P, $n = 8$). SEF95 and BIS were significantly increased by ketamine injection, as well as by emergence, compared with baseline values ($P < 0.05$, each case). AMP decreased significantly at emergence when compared with EEG activation induced by ketamine. ($P < 0.05$, Keta PK vs. Eme_P). The finding that ketamine increased SEF95 and BIS, similar to the changes observed during the emergence phase, but with a degree of activation less than that during emergence, showed that the activated common EEG indices exhibited no characteristic features specific to ketamine.

Figures 2 and 3 show raw EEG data and the corresponding power spectra, respectively, before and 15 min after injection of ketamine in a representative case in Group PK (A: Base_PK, B: Keta_PK) and after discontinuation of administration of propofol in Group P without administration of ketamine (C: Eme P). We found a remarkable shift of the peak in the α-range to a higher frequency with administration of ketamine (shown by arrows in Fig. 3), but disappearance of the peak in the emergence phase.

Figure 4 shows the average normalized power spectra during propofol-TCI in both groups (A: Base_P & PK, $n = 17$), 15 min after injection of ketamine (B: Keta_PK, $n = 9$), and after interruption of propofol injection (C: Eme_P, $n = 8$), respectively. Administration of ketamine shifted the power spectrum of the EEG under propofol anesthesia to a higher frequency, resulting in peaks at about 15 Hz, instead of spindle peaks at 10 Hz. On the other hand, discontinuation of propofol increased relative power in the higher frequency range (above 30 Hz, γ-range), but did not induce compensatory α-peaks.

Table 2

EEG variables under propofol-TCI.

Group	Group P & PK	Group PK		Group P	
Point	Base_P & PK	Base_PK	Keta_PK	Base_P	Eme_P
n	17	9		8	
SEF95 (Hz)	15.3 (14.7, 16.0)	15.3 (14.8, 16.0)	21.0 (20.2, 21.4)*	15.3 (14.7, 15.3)	22.7 (22.0, 27.3)*
BIS	42.6 (40.7, 47.2)	42.8 (41.9, 47.3)	67.2 (63.6, 69.7)* **	42.6 (40.7, 47.2)	95.3 (81.4, 96.3)*
AMP (μv)	11.1 (9.1, 11.7)	11.1 (9.1, 11.7)	10.9 (9.4, 11.8)**	11.1 (9.1, 11.7)	7.9 (7.5, 9.7)*

Values are presented as median (with 25% and 75% percentile).
Base_P & PK, during propofol-TCI in both groups ($n = 17$); Base_PK, during propofol-TCI in Group PK ($n = 9$), Base_P, during propofol-TCI in Group P ($n = 8$); Keta_PK: 15 min after addition of ketamine to propofol-TCI in Group PK ($n = 9$); Eme_P, emergence after discontinuation of propofol in patients not receiving ketamine in Group P ($n = 8$). SEF95, spectral edge frequency 95%; BIS: bispectral index, AMP, mean amplitude. *$P < 0.05$, Base_PK vs. Keta_PK, Base_ P vs. Eme_P. **$P < 0.05$. Keta_PK vs. Eme_P.

The mean peak frequencies at four time points before and after injection of ketamine (baseline, and 15, 30, and 45 min after injection of ketamine) in Group PK are shown in Fig. 5. With propofol alone, the peak of the spindle waves was in the α-range, with an average of 10.4 ± 0.9 Hz (baseline: Base_PK). Approximately 15 min after ketamine was injected intravenously, the peak shifted to 15.1 ± 1.4 Hz

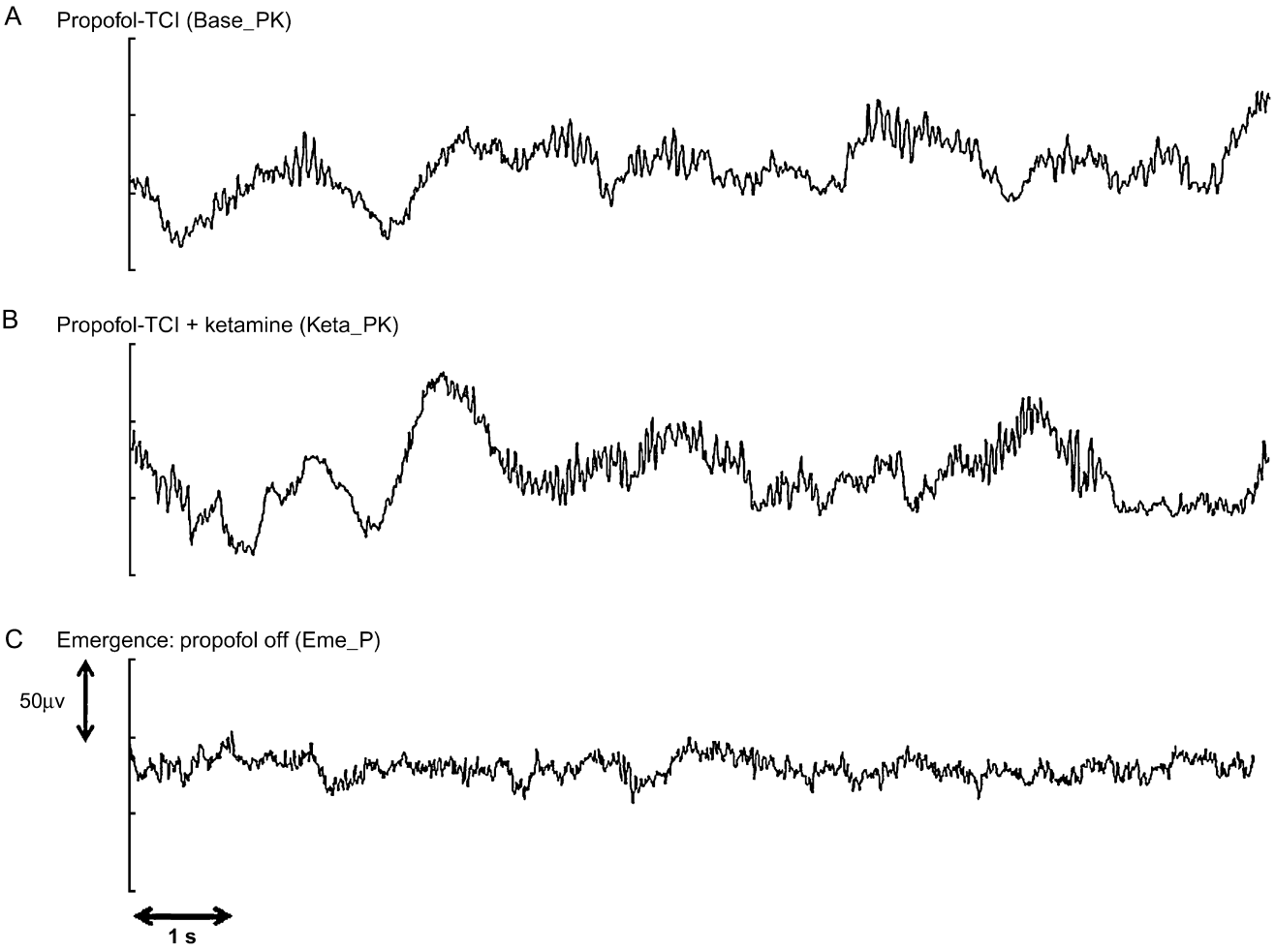

Fig. 2. A set of representative raw electroencephalogram (EEG) data. (A) During propofol-TCI in Group PK (Base_PK), (B) approximately 15 min after injection of ketamine during propofol-TCI in Group PK (Keta_PK).(C) Process of emergence after discontinuation of propofol-TCI in Group P (Eme_P).

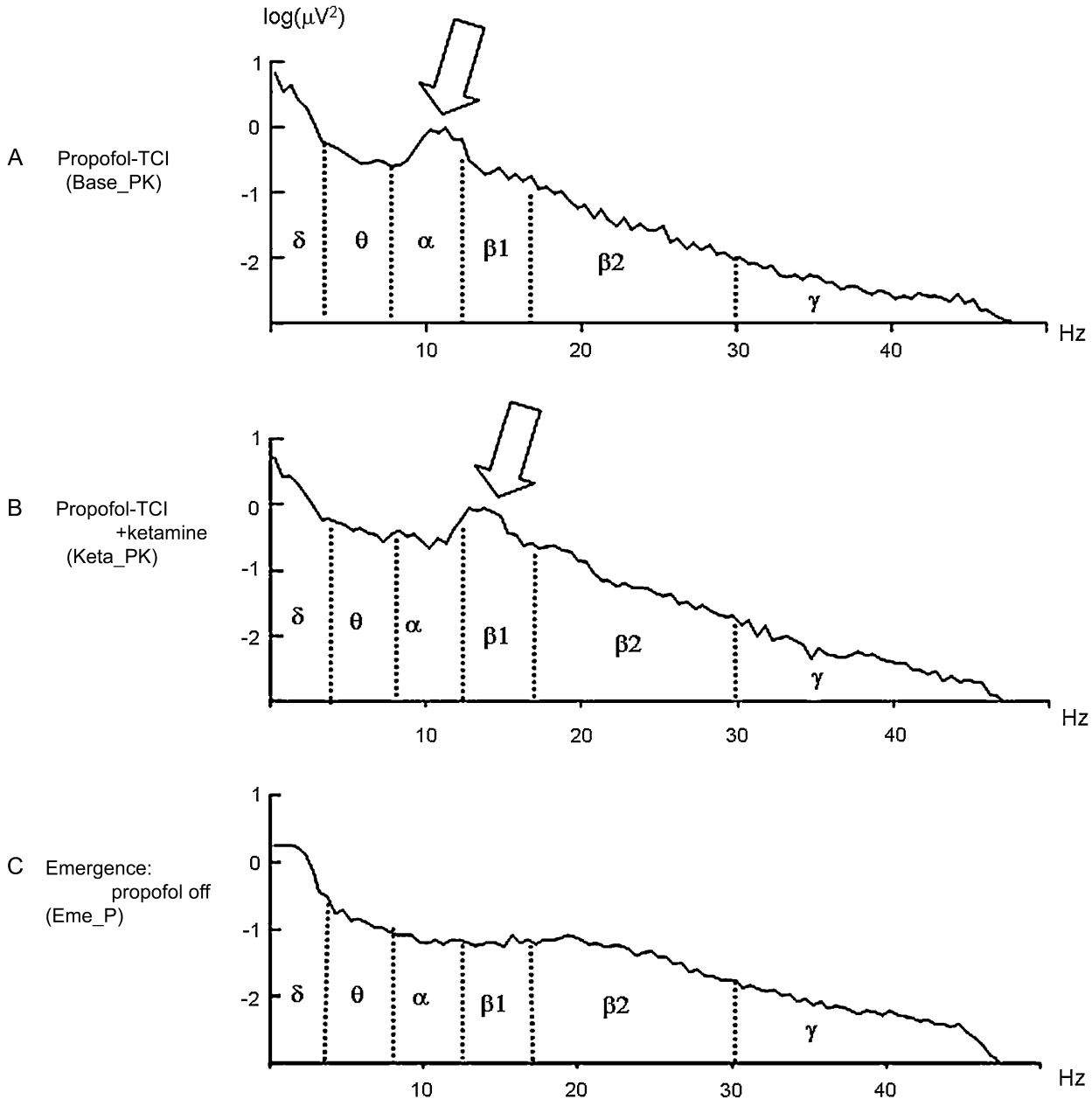

Fig. 3. Representative changes in power spectrum before and after injection of ketamine and after interruption of propofol-TCI. White arrows indicate spindle peaks. (A) During propofol-TCI anaesthesia, sleep spindles of around 10 Hz become predominant on the electroencephalogram (EEG) (Base_PK). (B) Approximately 15 min after injection of ketamine during propofol-TCI, a marked shift of the peak in the α-range to a higher frequency is noted (Keta_PK). (C) Process of emergence after discontinuation of propofol. Disappearance of the peak in the awakening phase is noted (Eme_P).

(Keta_PK. $P < 0.05$). The largest shift occurred approximately 15 min after ketamine injection, but the peak subsequently gradually returned towards the pre-ketamine level (Fig. 5). The shifts in the peaks were significant for each pair of 15-min intervals. This peak shifting occurred consistently in all patients, as reflected by stable and small coefficients of variation (CV) compared with baseline, especially at 15 and 45 min after administration of ketamine (Fig. 5).

Table 3 show the changes in the normalized power spectrum with respect to each frequency band (δ, θ, α, β1, β2, and γ) during propofol-TCI-anesthesia (Base_P & PK, Base_PK, Base_P), 15 min after administration of ketamine in Group PK (Keta_PK, $n = 9$), and after interruption of propofol in Group P

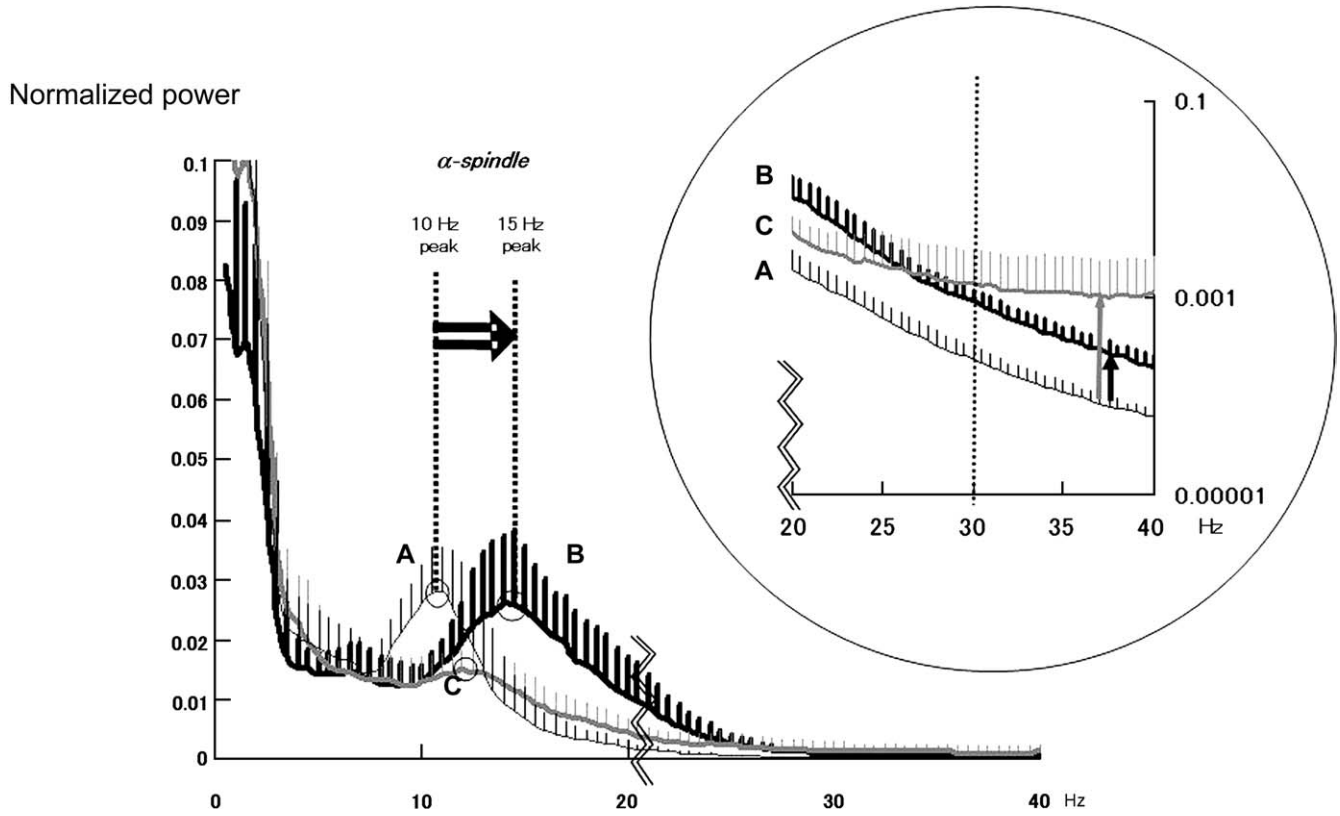

Fig. 4. Averages of normalized power spectra with standard deviation (SD) are shown during (A) thin line: propofol-TCI in both Group P and Group PK (Base_P & PK, Group-P & PK n = *17), (B) bold line: 15 min after ketamine administration (Keta_PK, Group PK,* n = *9) and (C) gray line: process of emergence after discontinuation of propofol administration (Eme_P, Group P,* n = *8). SDs are shown as perpendicular lines. Power spectra are in a normalized form, i.e. the ratio of individual power to total power within the frequency range from 0.5Hz to 47.0Hz at every 0.5-Hz interval. The inside of the circle at the upper right hand corner shows a magnified version of the same figure with a logarithmic scale for enhanced presentation of the higher frequency area above 20 Hz.*

(Eme_P, $n = 8$). After administration of ketamine, the normalized power in the α-range decreased significantly ($P < 0.05$). On the other hand, normalized power in the β1-, β2- and γ-ranges increased significantly. However, the EEG activation induced with ketamine differed from that during the emergence phase after discontinuation of propofol, in that the increase in normalized power in the β1-range was larger in the ketamine group than during emergence from propofol anesthesia ($P < 0.05$) but the increase in normalized power in the γ-range was smaller than that in the emergence period ($P < 0.05$).

Discussion

As some features of EEG activation by ketamine, i.e. increases in β-activity, BIS and SEF95 (5–7,21–24), have already been described, we compared the activating effect of ketamine on EEG indices with the activation associated with the process of emergence. Changes in EEG variables with ketamine administration bore some resemblance to the arousal EEG, and there were no specific features compared with the emergence process, making it difficult to distinguish the two EEGs on the basis of common EEG variables such as BIS and SEF95 alone. It was thus necessary to explore in detail the features of EEG activation induced by NMDA-antagonism.

Although it is known that ketamine increases β-activity, the detailed pattern of this increased β-activity in the power spectrum has not yet been clarified. The present study showed for the first time that NMDA receptor antagonism with ketamine during coexisting administration of a $GABA_A$-agonist, propofol, resulted in the shift of the α-peaks to the frequencies approximately 5 Hz higher, from the α area to the β1 area of the power spectra. It suggests that β-activity increased because of the increases in the frequencies constituting the α waves by approximately 5 Hz. The nature of neural synchronization is commonly associated with two processes: the first process is related to changes in the amplitude of

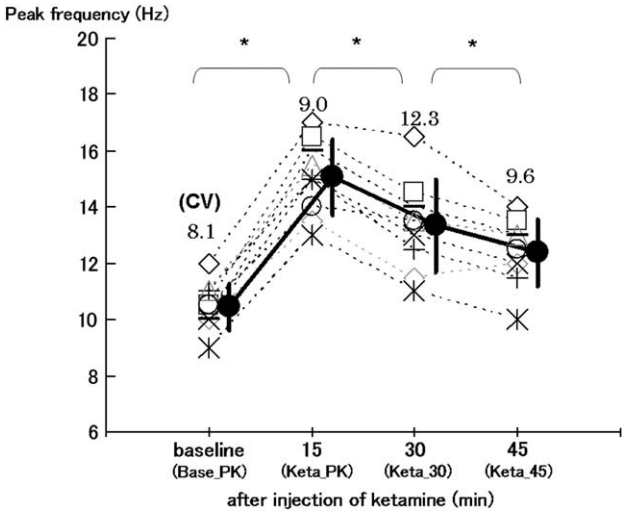

*Fig. 5. The mean peak frequencies at four time points before and after injection of ketamine (baseline: before injection of ketamine, 15, 30, 45: at 15 min, 30 min and 45 min after injections of ketamine) in Group PK are shown. Coefficients of variation (CV% = 100*SD/mean) are indicated for each point. Each different symbol in the figure means the individual data of the person employed in the study* (n = *9).* *A statistically significant difference was found between the measuring pairs between 15-min intervals ($P < 0.05$).

neural oscillations, with increases or decreases in amplitude depending on the number of active neurons firing in synchrony (15), which, in turn, can be detected by synchronous high peaks on power spectral analysis; the other process of neural synchronization involves phase synchronization, which is a manifestation of the non-linear nature of neural activity. Therefore, the synchronous neural activity of α spindle waves appears in the α-peaks on the power spectrum as well as in phase analysis. These results, that ketamine induced the shift of the α-peaks to higher frequencies, and that the relative powers of the shifted peaks were the same as those of the α-peaks, are particularly notable, because these findings have the possibility to suggest that α spindle rhythm may be modulated by an NMDA-antagonist. Moreover, returns of the shifted peaks over time towards baselines were also observed, suggesting the reproducibility of these phenomena.

Conversely, although ketamine shifted the α-peaks to the β-band, the α-peaks disappeared in the emergence phase. Hence, our study showed that addition of ketamine to propofol affected the oscillatory features of α-waves by a mechanism other than withdrawal of anesthetics, although suppression of the EEG by propofol is in a sense competed with ketamine. Although our results could not directly explain the neuro–physiological interaction between NMDA and $GABA_A$ mechanisms on α-spindles, we have a possible hypothesis that ketamine modulates the $GABA_A$ subcortical system. Because the rhythmic spindle frequency (7–14 Hz) initiated in RE neurons is determined with the duration of the hyperpolarization in the TC cells, and because the alterations of wide variety of ionic currents with different voltage dependencies and kinetics of activation/inactivation with different inhibitory time constants contribute to the duration of hyper-polarization (11–13, 25–29), thus minor alterations of these membrane potential in RE and TC induced by ketamine have the possibility to well account for the change of the spindle frequency. However, it is one of our possible speculations. Further study is needed to clarify the interaction between NMDA and $GABA_A$ mechanisms, as spindle oscillations progressively develop as a consequence of membrane potential changes in TC and RE thalamic cells (25–29), and linking neurosystems can interfere with membrane resting potential through this integrated complex network. Finally, if ketamine increases the frequencies of α-spindle waves without blocking their formations, the

Table 3

Changes in normalized power spectrum with respect to each frequency band (δ, θ, α, β1, β2 and γ).

Group	Group P & PK	Group PK		Group P	
Point	Base_P & PK	Base_PK	Keta_PK	Base_P	Eme_P
n	17	9		8	
δ	55.2 (46.1, 60.7)	51.4 (40.6, 59.9)	31.5 (29.6, 35.8)	59.2 (52.9, 65.6)	50.8 (31.2, 57.3)
θ	13.9 (11.7, 15.5)	14.0 (13.0, 14.7)	11.2 (8.7, 13.8)	12.0 (9.4, 16.8)	9.8 (8.6, 11.5)
α	22.4 (17.6, 26.8)	24.1 (19.4, 31.8)	15.8 (12.2, 17.6)*	20.3 (17.2, 22.4)	11.6 (7.5, 14.5)*
β1	5.6 (4.9, 7.0)	5.6 (5.1, 10.8)	24.2 (20.8, 26.8)* **	5.3 (4.3, 6.1)	11.0 (5.2, 14.4)
β2	2.3 (1.9, 2.7)	2.4 (2.2, 3.1)	11.9 (8.6, 12.8)*	2.0 (1.7, 2.7)	8.2 (5.8, 19.4)*
γ	0.31 (0.25, 0.34)	0.31 (0.26, 0.34)	0.93 (0.82, 1.26* **)	0.29 (0.24, 0.32)	7.32 (3.03, 15.10)*

Values are the median (with 25% and 75% percentile). *$P < 0.05$, Base_PK vs. Keta_PK, Base_ P vs. Eme_P. **$P < 0.05$, Keta_PK vs. Eme_P.

sedative effect through the TC system may be kept, whereas EEG is apparently activated.

The modified Marsh models used in the TCI-system were found to produce good performance and to be appropriate for propofol-TCI within the range of 3–6 μg/ml, with small bias and little inaccuracy (30). However, there may be unavoidable prediction errors that are influenced by pharmacokinetic variability among and within patients, as the TCI system uses averaged pharmacokinetic models derived from population samples. We checked the level of epidural analgesia and clearly ascertained its effectiveness in the presented cases. Nevertheless, it was not possible to completely exclude effects of surgical stimulation on the EEG. Furthermore, measurements of the EEG during anesthesia were probably little affected by muscle activity, as sufficient muscle relaxant was administered. However, during measurements of the EEG in awaking phase, effects of muscle activity cannot be completely eliminated, although we confirmed little activity on the EMG indication bar during BIS monitoring, which can detect high-frequency, 70–110 Hz artifacts. This is a limitation of this study.

In conclusion, we found that propofol caused α oscillations at 10 Hz frequencies, and that ketamine shifted them to approximately 5 Hz higher frequencies, suggesting the possibility that ketamine interacts with the spindle oscillations induced by a GABA agonist.

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