Dopamine D2-receptor Antagonist Droperidol Deepens Sevoflurane Anesthesia

Ryuhei Araki, M.D., Kazuko Hayashi, M.D., Ph.D., Teiji Sawa, M.D., Ph.D.

ABSTRACT

Background: Although midbrain dopaminergic pathways are known to contribute to arousal and emergence from anesthesia, few reports exist regarding the anesthetic effects of dopamine D2 receptor antagonism in humans. This study examined the effect of the D2 receptor antagonist droperidol on sevoflurane anesthesia by examining α and slow wave electroencephalogram oscillations.

Methods: Forty-five patients, age 20 to 60 yr, were enrolled. Frontal electroencephalograms were continuously collected for offline analysis *via* Bispectral Index monitoring. After induction of anesthesia, end-tidal sevoflurane concentration was deliberately maintained at 1%, and intravenous droperidol (0.05 mg/kg bolus) was administered. Electroencephalogram changes were examined in power spectrum and bicoherence, before and 10 min after droperidol injection, then compared using the Wilcoxon signed-ranks test and/or paired *t* test.

Results: Droperidol significantly augmented the α-bicoherence peak induced by sevoflurane from 30.3% (24.2%, 42.4%) to 50.8% (41.7%, 55.2%) (median [25th, 75th percentiles]; $P < 0.0001$), Hodges-Lehman median difference, 15.8% (11.3 to 21.4%) (95% CI). The frequency of the α-bicoherence peak was simultaneously shifted to the lower frequency; from 11.5 (11.0, 13.0) to 10.5 (10.0, 11.0) Hz (median [25th, 75th percentiles], $P < 0.0001$). Averaged bicoherence in the δ-θ area increased conspicuously from 17.2% (15.6 to 18.7%) to 25.1% (23.0 to 27.3%) (mean [95% CI]; $P < 0.0001$), difference, 8.0% (6.0 to 9.9%).

Conclusions: Droperidol augments both α and δ-θ bicoherences while shifting the α-bicoherence peaks to lower frequencies, and enhances the effect of sevoflurane anesthesia on the electroencephalogram *via* γ-aminobutyric acid–mediated oscillatory network regulation. **(Anesthesiology 2018; 128:754-63)**

MIDBRAIN dopaminergic neurons are implicated in arousal-promoting pathways, as well as in the cholinergic, histaminergic, noradrenergic, and orexin networks.[1] Dopamine release by neurons in the ventral tegmental area was recently reported to induce emergence from general anesthesia *via* the dopamine D1 receptor.[2–4] The ventral periaqueductal gray matter also provides wake-active neurons, a major ascending dopaminergic pathway involved in arousal.[5,6] Dopamine is thus of particular interest when considering arousal responses and/or emergence from general anesthesia. However, few reports have investigated the effects of dopaminergic systems on maintenance or deepening of general anesthesia.

Several studies have reported that droperidol, a dopamine D2 receptor antagonist, reduces Bispectral Index (BIS) values during sevoflurane anesthesia in humans at lower doses than those required for neuroleptanesthesia. This has also been reported with spinal anesthesia combined with propofol sedation, although detailed information regarding the electroencephalogram changes are currently unknown.[7,8]

The majority of D2 receptors are found on postsynaptic nondopaminergic neurons, including γ-aminobutyric acid–mediated (GABAergic) neurons as heteroreceptors.[9] These include dopamine receptors in the ventral mesencephalon, found on γ-aminobutyric acid (GABA)–secreting nondopaminergic neurons. Generally, dopamine acts on the D2 heteroreceptors of these GABAergic neurons, causing hyperpolarization, resulting in increased activity within the neural network by decreasing inhibitory GABA activity.[10,11] Since the dopaminergic pathway is linked to various regions of the brain, such as the thalamus, dorsal raphe, locus coeruleus, basal forebrain, ventrolateral preoptic nucleus, and prefrontal cortex, D2 receptor antagonism may directly influence general anesthesia *via* these neural networks.

GABAergic anesthetic agents promote α and δ-θ activity in the electroencephalogram, associated with neural network regulation and resonance of the thalamocortical and

What We Already Know about This Topic

- The administration of droperidol, a dopamine and adrenergic antagonist, can deepen anesthesia, as measured by the Bispectral Index, produced by the γ-aminobutyric acid–mediated volatile agents and propofol
- γ-Aminobutyric acid–mediated agents manifest thalamocortical oscillatory activity, and it is possible that droperidol enhances this activity

What This Article Tells Us That Is New

- Administration of droperidol decreased Bispectral Index values, augmented both α and δ-θ bicoherences, and shifted α-bicoherence to lower frequencies
- These data suggest that droperidol enhances sevoflurane's effect on the electroencephalogram, partly *via* γ-aminobutyric acid–mediated subcortical reverberating networks

Presented at the 10th International Symposium on Memory and Awareness in Anesthesia (MAA10), June 19 to 21, 2017, Helsinki, Finland.

Submitted August 2, 2017. Accepted November 24, 2017. From the Kyoto Chubu Medical Center, Kyoto, Japan (R.A., K.H.); and Kyoto Prefectural University of Medicine, Kyoto, Japan (R.A., K.H., T.S.).

 Anesthesiology 2018; 128:754-63

<zdoi;10.1097/ALN.0000000000002046>

corticothalamic axons.[12–16] In the nonlinear reverberating system between the cortex and thalamus, the output signal from the reverberating circuit should self-modulate by reentering the system as an input signal. This self-modulation comprises intermodulation products (the signal component produced by multiplication of the reentrant signals), resulting in quadratic phase coupling between the wave components in a signal. We previously indicated that bicoherence (the normalized bispectrum) can reveal the reverberating components of the thalamocortical reverberant network, representing massive synchronizations by detecting the intermodulation products and quadratic phase coupling.[17,18] The GABAergic anesthetics propofol, sevoflurane, desflurane, and isoflurane all show a certain unified pattern in the α and δ-θ area in the bicoherence spectra depending on the level of anesthesia by manifesting thalamocortical oscillatory activity *via* GABAergic pathways.[19–22] Accordingly, bicoherence analysis is suitable for understanding the level of anesthesia related to GABAergic mechanisms.

This study examined the effect of a dosage of the D2 receptor antagonist droperidol, lower than that typically required for neuroleptanesthesia, on sevoflurane anesthesia by analyzing continuous electroencephalogram bicoherence before and after droperidol injection. We hypothesized that droperidol deepens sevoflurane anesthesia, and that it alters the electroencephalogram and bicoherence pattern by enhancing reverberating oscillations characteristic of a GABAergic mechanism.

Materials and Methods

Protocol

This study was approved by the Institutional Review Board for Human Experiments at Kyoto Chubu Medical Center (Kyoto, Japan). We enrolled patients scheduled for general anesthesia in Kyoto Chubu Medical Center from January 2017 to March 2017, between the ages of 20 and 60 yr. Patients were excluded if they had a history of neurologic disease and/or QT interval prolongation (QTc ≥ 0.45). Two cases were excluded because surgery commenced before depth of anesthesia could be assessed in accordance with our protocol. We were able to analyze data from 45 patients (22 men, 23 women). According to our previous studies concerning the similar anesthesia level,[17,21–23] the SD of α bicoherence was at most 15; a sample size of 45 subjects per group is therefore adequate for statistical significance with a power of 0.8 and a significance level of 0.05. Mean age (SD) was 39 (3) yr, with age ranging between 20 and 58 yr, and weight (SD) was 63 (15) kg. Written, informed consent was obtained from all patients before participation.

Patients did not receive premedication. Anesthesia was induced using propofol (1 mg/kg) combined with sevoflurane (end-tidal concentration, 2%), remifentanil ($0.3\ \mu g \cdot kg^{-1} \cdot min^{-1}$), and fentanyl (2 μg/kg). Rocuronium was administered to obtain appropriate muscle relaxation. All patients were intubated and ventilated. Immediately after tracheal intubation, the sevoflurane end-tidal concentration and remifentanil infusion rate were changed to 1% and to $0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$, respectively. Anesthesia was maintained with sevoflurane and remifentanil at the same dosages. A BIS sensor (Quatro sensor, Aspect Medical Systems, USA) was mounted on the forehead and connected to an A-2000 BIS monitor (version 4.0, Aspect Medical Systems). Raw electroencephalograms (converted from analog to digital at 128 Hz) were continuously sampled from an A-2000 BIS monitor for offline analysis using Bispectrum Analyzer (BSA) version 3.22B2 software *via* an RS232 interface on a personal computer (CF-MX3, Panasonic, Japan).[24]

Approximately 15 min later, after the end-tidal sevoflurane concentration had been deliberately kept constant (1%), intravenous droperidol (0.05 mg/kg) was administered by bolus. The dose of droperidol (0.05 mg/kg) in this protocol was determined by our previous clinical experience. In our hospital, we have conventionally used a fixed dose of 2.5 mg droperidol in patients without QT prolongation, mainly for antiemetic purposes. We noticed in these instances that the BIS index decreased after 2.5 mg of droperidol injection, which sparked our interest in this phenomenon. Accordingly, we used an approximately equivalent dosage of droperidol in this protocol. Electroencephalogram analyses (power spectrum analysis and bicoherence analysis) were retrospectively performed at just before and then 10 min after droperidol injection, from the collected electroencephalogram data. Systolic arterial blood pressure and heart rate were maintained at greater than 90 mmHg and greater than 44 beats/min, respectively, using phenylephrine and atropine as required. Data collection for analysis was completed before the start of surgery.

Data Acquisition and Calculation

Electrode impedance was checked every 10 min and was maintained at 5 kΩ or lower throughout the study using the A-2000 BIS monitor. Signals less than 0.5 Hz or greater than 50 Hz were excluded. The spectral edge frequency 95 (SEF95) and BIS index values were simultaneously collected with the A-2000 every 60 s. The power spectrum was calculated from the preceding electroencephalogram over 1-min periods at 0.5 Hz intervals using BSA. Average power and bicoherence in the δ-θ area were calculated in the respective spectra under 6 Hz.

Bicoherence Calculation

Bicoherence values were computed in all pairs of frequencies between 0.5 and 20 Hz at 0.5 Hz intervals from the preceding 3-min period of artifact-free signals, and were represented as two-dimensional moving averages. These were calculated using nine points of bicoherence every 0.5 Hz, from 1.5 to 20.0 Hz, similar to the calculation method described in our previous studies.[17,21,23] The 3-min-long electroencephalogram signals were divided into a series of 2-s epochs, with

each epoch overlapping by 75%, resulting in 360 epochs. After applying the Blackman window function to the respective epoch, bicoherence $BIC(f_1, f_2)$ values were calculated using the following equations:

sum of absolute triple product:

$$sTP(f_1, f_2) = \sum_{i=1}^{L} \left| X_i(f_1) X_i(f_2) X_i^*(f_1 + f_2) \right|$$

$$bispectrum: B(f_1, f_2) = \left| \sum_{i=1}^{L} X_i(f_1) X_i(f_2) X_i^*(f_1 + f_2) \right|$$

$$BIC(f_1, f_2) = 100 \frac{B(f_1, f_2)}{sTP(f_1, f_2)}$$

j: epoch number

$X_j(f_1)$: complex value calculated by Fourier transformation of the *j*th epoch

$X_i^*(f_1 + f_2)$: conjugate of $X_i(f_1 + f_2)$

Computations were performed using MATLAB software (version 8.4.0.150421 [R2014b], MathWorks, USA). The bicoherence spectra were then presented around the diagonal lines (the same pairs of the frequencies), as shown in figure 1.

Statistical Analysis

Comparison was made between the data collected before and then at 10 min after injection of droperidol from electroencephalogram parameters (BIS, SEF95; both frequencies causing the α power peak and the α bicoherence peak; α power peak and the α bicoherence peak). Nonparametric analysis (Wilcoxon signed-rank test) was performed as the distribution indices were not necessarily regarded as normal according to the Shapiro–Wilk normality test. Shifts of averaged δ-θ in the power (logarithmic form) and bicoherence spectra were analyzed using a paired *t* test, as the distributions were regarded as normal. Predictive Analysis Software (IBM SPSS Statistics version 23.0, SPSS, Japan) was used for statistical procedures. The results were presented as median (25th, 75th percentiles), or means (95% CI). The difference values of $P < 0.05$ were considered significant. The difference in medians with 95% CI was examined by the Hodges-Lehman method using R: A Language and Environment for Statistical Computing (R Core Team [2017], R version 3.4.2, R Foundation for Statistical Computing, Austria, http://www.R-project.org/).

Results

Two representative time courses of power and bicoherence spectra before and after droperidol injection in a 47-yr-old woman and a 50-yr-old woman are shown in figures 2 and 3. The raw electroencephalograms and the corresponding power and bicoherence spectra in the respective patients at just before and about 10 min after injection of droperidol are also shown. Several minutes after droperidol injection, the electroencephalograms changed gradually, then reached approximately maximum effect: the α-bicoherence peak was augmented, the α peaks in both the power and bicoherence spectra shifted to the lower frequency, the δ power increased, and the peak bicoherence in the δ-θ area increased. The continuous augmentation of α-bicoherence and continuous shift of the α-bicoherence peak to the lower frequency induced by droperidol (figs. 2 and 3) are noteworthy, because these results suggest the changes are due to the functional modulation of the same reverberant source.

Figures 4 and 5 show the summary of electroencephalogram results in 45 cases. Approximately 10 min after droperidol injection, the electroencephalogram variables BIS and SEF95 were significantly decreased from 59 (57 to 60) and 18.0 (17.3 to 18.7) Hz to 42 (40 to 44) and 13.5 (13.0 to 14.1) Hz (mean [95% CI], $P < 0.0001$ for each), mean difference (95% CI), –17 (–18 to –15) and –4.5 (–4.8 to –4.1) Hz. Both α peak values in power and bicoherence were significantly augmented from 1.97 (1.26, 3.68) μV^2 and 30.3% (24.2%, 42.4%) to 3.07 (1.53, 5.26) μV^2 and 50.8% (41.7%, 55.2%) (median [25th, 75th percentiles], $P = 0.002$ for power, $P < 0.0001$ for bicoherence), Hodges-Lehman median difference (95% CI), 0.83 (–0.02 to 1.75) μV^2 and 15.8% (11.3 to 21.4%). Simultaneously, the frequency causing α peaks in the power and bicoherence spectra decreased significantly from 12.0 (11.0, 12.5) and 11.5 (11.0, 13.0) Hz to 10.5 (9.5, 11.0) and 10.5 (10.0, 11.0) Hz, respectively ($P < 0.0001$ for each), Hodges-Lehman median difference, –1.5 (–2.0 to –1.0) and –1.5 (–2.0 to –1.0) Hz. Averaged power and bicoherence in the δ-θ area increased conspicuously from 0.252 (0.167 to 0.336) log(μV^2) and 17.2% (15.6 to 18.7%) to 0.680 (0.600 to 0.760) log(μV^2) and 25.1% (23.0 to 27.3%) ($P < 0.0001$ for each), mean difference, 0.428 (0.363 to 0.494) log(μV^2) and 8.0% (6.0 to 9.9%), respectively.

Figure 6 shows the 45 superimposed power and bicoherence spectra around diagonal lines at just before and approximately 10 min after droperidol injection, as the average with 95% CI. Again, α peaks in the bicoherence spectra increased. Simultaneously, both α peaks in the power and bicoherence spectra shifted to the lower frequencies. The averaged power and bicoherence in the δ-θ area increased.

Discussion

The findings of this study indicate that droperidol increases α bicoherence while simultaneously decreasing the basal frequency of α oscillation. The power and bicoherence in the δ-θ area are also significantly increased by droperidol. In general, along with deepening GABAergic general anesthesia from light (defined as BIS of about 60, and/or 1% sevoflurane) to moderate levels (defined as BIS of about 40, and/or 2% sevoflurane), α-bicoherence is augmented and the frequency causing the α-bicoherence peak decreases. Slow wave activity increases simultaneously. At deep levels of anesthesia (defined as BIS of about 30, and/or 3% sevoflurane), α bicoherence

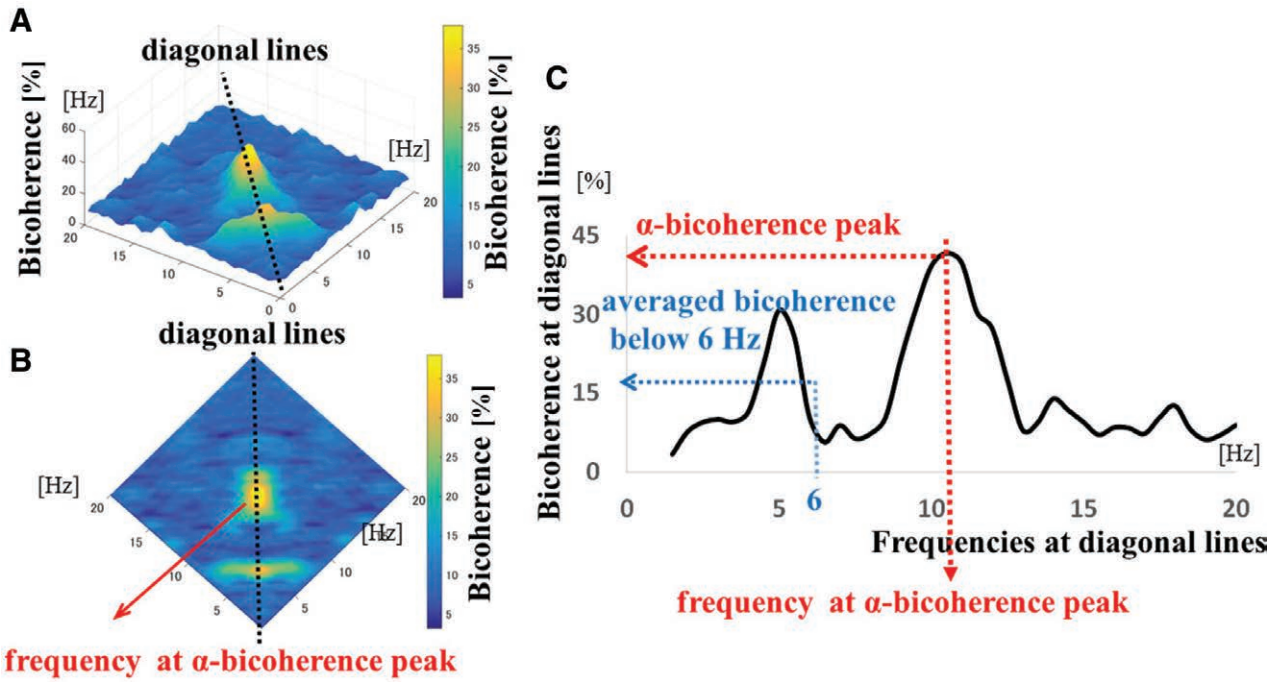

Fig. 1. (*A* and *B*) Bicoherence computed in all pairs of frequencies are averaged around the *diagonal lines* (same pairs of frequencies). (*C*) The bicoherence spectrum is obtained as related to the same pairs of the frequencies in the *diagonal line*.

finally decreases with a predominance of slow waves and further increases in δ-θ bicoherence.[17–22] The current findings are similar to the electroencephalogram changes induced by deepening light 1% sevoflurane anesthesia to a moderate 2% level, which mainly affects the GABAergic pathway.[17] Although sevoflurane is known to bind to various other targets in the central nervous system, such as *N*-methyl-D-aspartate, glycine, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, acetylcholine, potassium channels, and serotonin receptors, GABAergic inhibition is recognized as the dominant mechanism of action of sevoflurane anesthesia, because the electroencephalogram during sevoflurane anesthesia shows δ-θ and α oscillations similar to propofol.[25–28]

These coherent δ-θ and α oscillations are known to occur in thalamocortical oscillations chiefly *via* the GABAergic pathway. Bicoherence, the normalized bispectral analysis, is capable of tracking changes in these reentry systems by quantifying the quadratic phase coupling between signals using a one-channel cortical electroencephalogram.[17–22] Because droperidol augmented α bicoherence and δ-θ bicoherence while simultaneously shifting the α bicoherence peak to a lower frequency in a sustained and graded manner, the resultant electroencephalogram changes were recognized as being induced by modification of the same subcortical reverberant source, namely thalamic reticular and thalamocortical neurons. Thus, droperidol, a dopamine D2 receptor antagonist, appeared to enhance sevoflurane anesthesia, partly through the same neural pathway of GABAergic mechanisms.

Five dopamine receptor subtypes (D1 to D5) have been identified in mammals. They are G protein–coupled receptors divided into two major groups: the D1-like receptors (D1, D5) and the D2-like receptors (D2, D3, D4). While activation of D1-like receptors increases excitability through activating adenylyl cyclase and increasing cyclic adenosine monophosphate levels, D2-like receptors are inhibitory *via* suppression of calcium ion influx with coupling of inhibitory G protein coupled receptors and inhibition of adenylyl cyclase.[9,29]

D2 receptors exist as autoreceptors on the terminals of dopamine neurons themselves, playing a key role in regulating the dopaminergic system by providing feedback inhibition. However, the majority of D2 receptors are found as heteroreceptors on postsynaptic nondopaminergic neurons, including GABA neurons.[9] Accordingly, we think that these D2 heteroreceptors may play a crucial role in the modulation of anesthesia induced by droperidol. Although the precise mechanism of droperidol's anesthetic effect has not been well studied, D2 receptor antagonism can increase inhibitory tone in the neural network of midbrain dopaminergic neurons *via* facilitation of inhibitory GABAergic interneurons.[10,11] This may explain how droperidol increases the depth of sevoflurane anesthesia.

Besides its dopaminergic actions, droperidol may affect anesthesia *via* its antagonistic effect on α1-adrenergic receptors. The main noradrenergic nerve nucleus, the locus coeruleus, and other noradrenergic nuclei such as the medial septal area, the medial preoptic area, and the lateral hypothalamus, are known to exert potent arousal-promoting actions, where α1- and β-adrenergic receptors are known to have important roles with conjugation of complex subcortical network and cortical innervations.[30–32] Additionally, α1

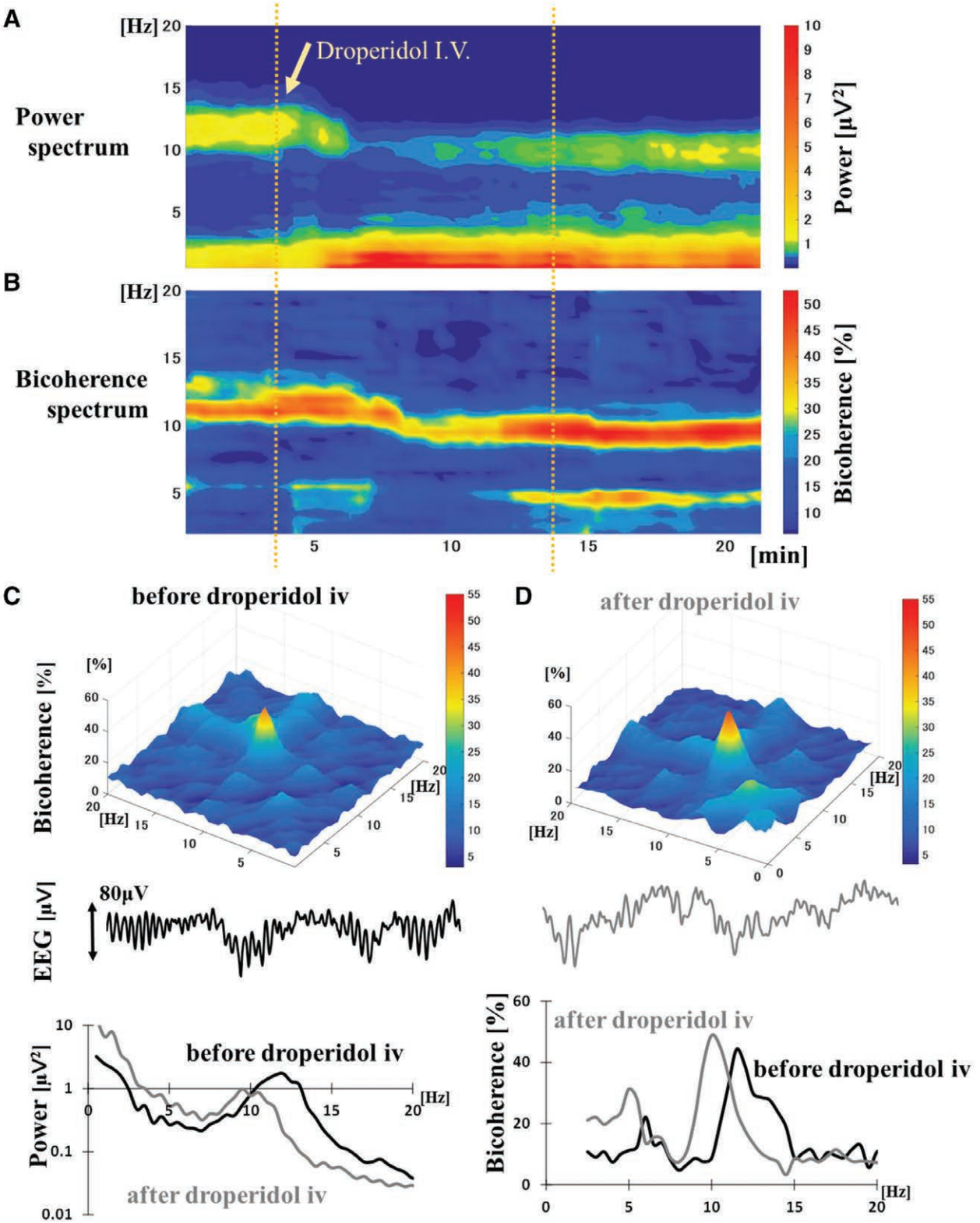

Fig. 2. A representative time course of power (*A*) and bicoherence (*B*) spectra before and after droperidol injection in a 47-yr-old woman. The raw electroencephalogram (EEG) and the corresponding power and bicoherence spectra at just before (*C*) and about 10 min after (*D*) injection of droperidol are also shown. *Black line*: before droperidol intravenous injection (iv) in value; *gray line*: after droperidol iv in value.

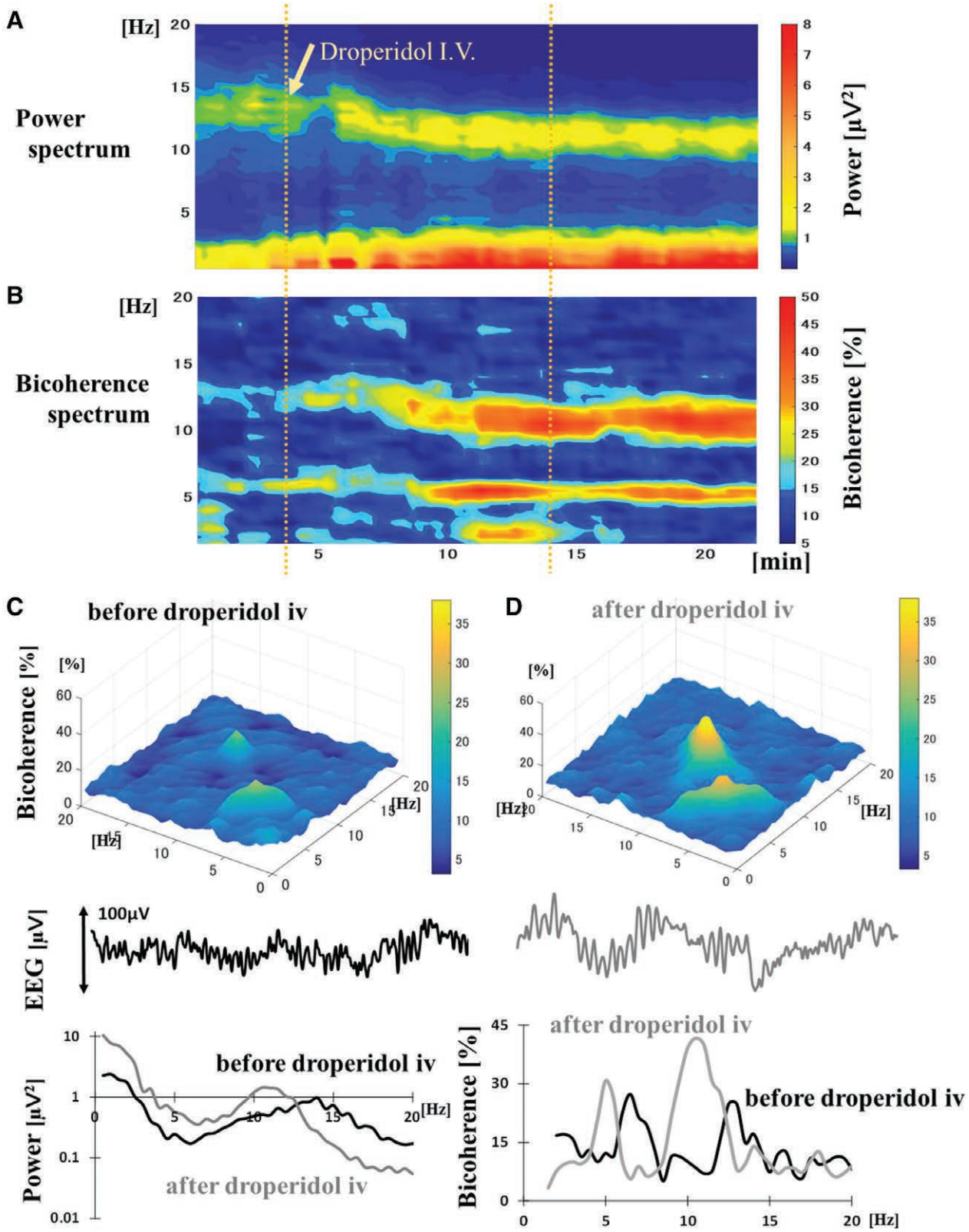

Fig. 3. A representative time course of power (*A*) and bicoherence (*B*) spectra before and after droperidol injection in a 50-yr-old woman. The raw electroencephalogram (EEG) and the corresponding power and bicoherence spectra at just before (*C*) and about 10 min after (*D*) injection of droperidol are also shown. *Black line*: before droperidol intravenous injection (iv) in value; *gray line*: after droperidol iv in value.

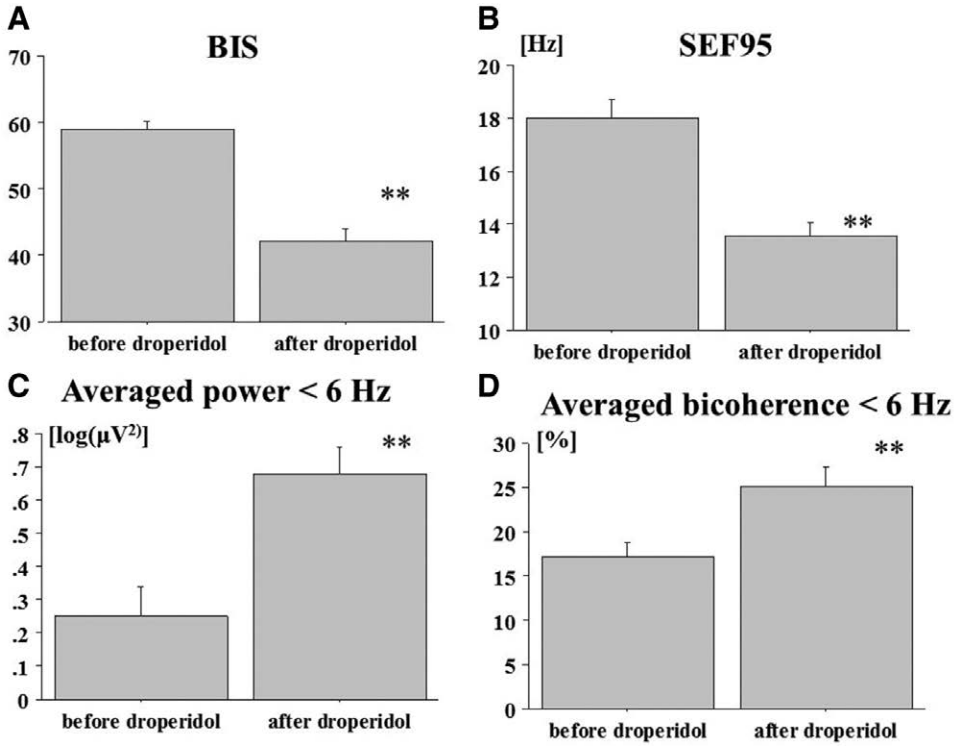

Fig. 4. Summary of bispectral index (BIS; *A*), spectral edge frequency 95 (SEF95; *B*), the averaged power of the logarithm indication (*C*) and bicoherence (*D*) lower than 6 Hz are shown as means with 95% CI in 45 cases. $^{**}P < 0.05$ for paired *t* test.

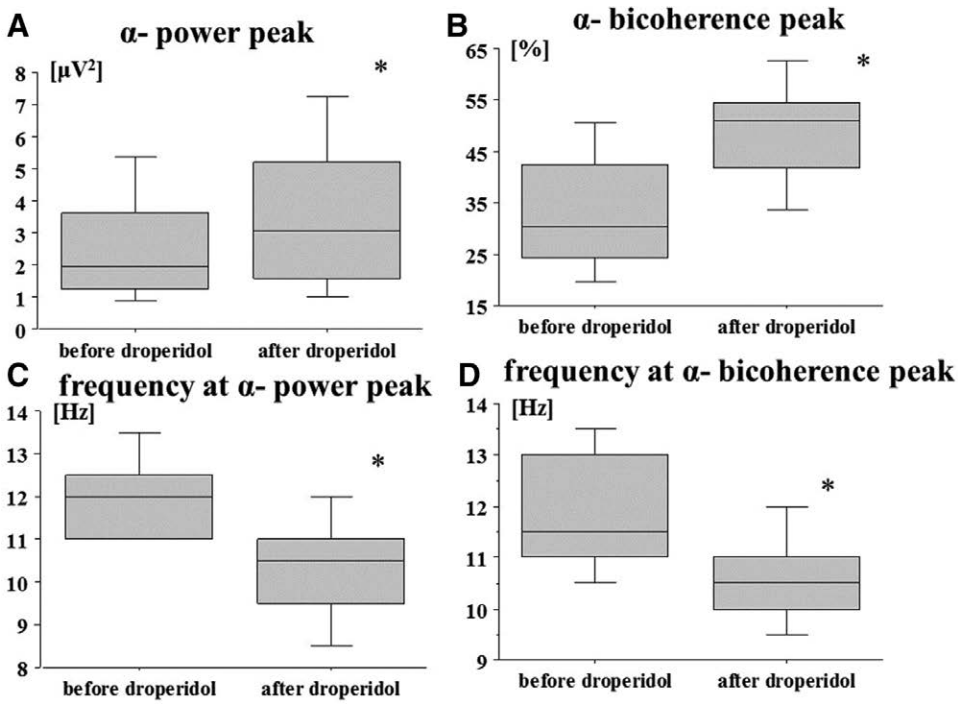

Fig. 5. Summary of α peaks in power and bicoherence spectra, shown as medians with 10th, 25th, 75th, and 90th percentiles in 45 cases. (*A*) α-Power peak; (*B*) α-bicoherence peak; (*C*) frequency at α-power peak; (*D*) frequency at α-bicoherence peak. $^{*}P < 0.05$ for Wilcoxon signed-rank test.

as well as α2 adrenoceptors in the dorsal raphe nucleus modulate the release of serotonin, which also influences anesthesia.[33] Thus, α1 blockade by droperidol also modulates sleep, anesthesia, and arousal responses, which may be included in the current results as an indirect influence on the GABAergic pathway.

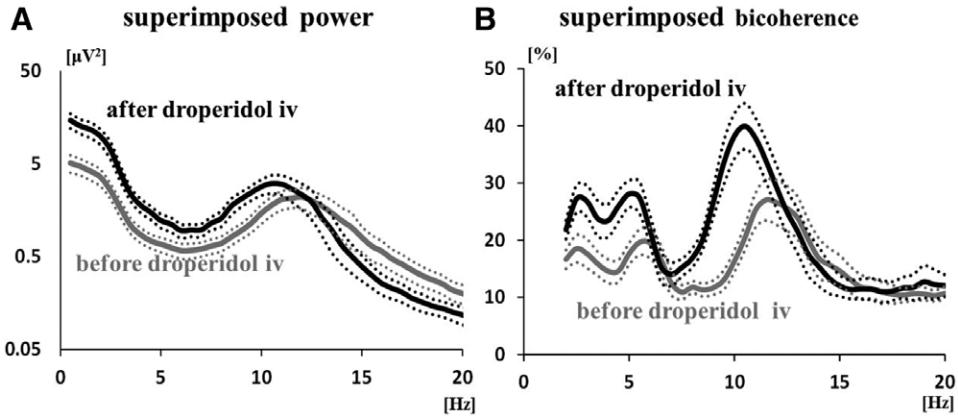

Fig. 6. The 45 superimposed power (*A*) and bicoherence spectra around *diagonal lines* (*B*) at just before and approximately 10 min after droperidol injection, shown as the average with 95% CI. *Black line*: before droperidol intravenous injection (iv) in value; *gray line*: after droperidol iv in value.

On the other hand, droperidol has been reported to induce adverse effects *via* its actions on the GABA-type A receptor itself, causing inhibition of the GABAergic response. Unwanted side effects, such as anxiety and dysphoria, were reported on emergence from droperidol neuroleptanesthesia, due to submaximal GABAergic inhibition.[34] Conversely, GABA has also recently been found to be released directly from dopaminergic axons, and may function as a cotransmitter in monoaminergic neurons in basal ganglia circuits.[35,36] Droperidol reportedly also has preferential nicotinic effects on neuronal nicotinic acetylcholine receptors, mediating neuroleptanesthesia.[34,37] Dopamine's important role in learning and reinforcement has also been revealed in midbrain dopaminergic neurons through glutamatergic signaling *via* an isoform of the vesicular glutamate transporter, although the function of glutamatergic synaptic transmission by dopaminergic neurons remains unclear.[36,38,39] As such, dopamine acts on complex neural network systems *via* a large number of mechanisms. In rats, Tanifuji *et al.* reported that droperidol does not alter minimum alveolar concentration of general anesthetics, although minimum alveolar concentration expresses the immobility produced by inhaled anesthetics, and does not necessarily equate with brain activity.[40] Since droperidol has various influences on arousal, sedation, consciousness, emergence, and depth of anesthesia, we consider that the current results reflect a primary, complex, and integrated effect that may be easily influenced by environmental and other factors. The current study was conducted using a relatively light plane of sevoflurane anesthesia of about 1%, where the BIS was about 60.

The dose of droperidol used was considerably higher than the current recommended dosages for antiemetic purposes (0.625 to 1.25 mg), which are not considered to pose a significant clinical risk for arrhythmias.[41] We used 2.5 mg of droperidol in a patient of 50 kg, as we have commonly used this dose for chiefly antiemetic purposes in our institution in patients without QT prolongation. At the time of writing, no arrhythmic complications related to droperidol have been documented at our hospital. Although our dose was much lower than that used for neuroleptanesthesia and sedation, we should have employed the lower antiemetic dosage if we wished only to provide prophylaxis against postoperative nausea and vomiting.

However, the remarkable electroencephalogram changes observed in this study were surprising, because lower doses of droperidol than those used for neuroleptanesthesia displayed a strong anesthetic effect. The simultaneous use of droperidol and GABAergic anesthetics such as sevoflurane and propofol may result in lower doses of GABAergic agents being needed to achieve the appropriate depth of anesthesia. This may have useful economic implications, as has been reported previously.[42] However, we were unable to obtain data later than 10 min after droperidol injection, because the initial depth of anesthesia was not maintained after surgery commenced. As such, we are unable to comment on how long the enhanced anesthetic effect of droperidol on sevoflurane anesthesia is maintained.

Conclusions

Droperidol, a dopamine D2 receptor antagonist, augmented both α and δ-θ bicoherences while shifting the α-bicoherence peaks to lower frequencies. There was a simultaneous increase in slow wave oscillation, suggesting that droperidol enhances the effect of sevoflurane anesthesia on the electroencephalogram, partly through GABAergic subcortical reverberating networks.

Acknowledgments

The authors thank Satoshi Hagihira, M.D., Ph.D. (Clinical Professor, Department of Anesthesiology, Kansai Medical University, Osaka, Japan), for supplying Bispectrum Analyzer (BSA) software.

Research Support

Supported by a Grant-in-Aid for Scientific Research (C) from the Japan Society for the Promotion of Science (JSPS KAKENHI No.15K10518), Tokyo, Japan.

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Hayashi: Yagi Ueno 25, Nantan, Kyoto, 629-0141, Japan. zukko@koto.kpu-m.ac.jp. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. Anesthesiology's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Monti JM, Monti D: The involvement of dopamine in the modulation of sleep and waking. Sleep Med Rev 2007; 11:113–33
2. Solt K, Van Dort CJ, Chemali JJ, Taylor NE, Kenny JD, Brown EN: Electrical stimulation of the ventral tegmental area induces reanimation from general anesthesia. Anesthesiology 2014; 121:311–9
3. Solt K, Cotten JF, Cimenser A, Wong KF, Chemali JJ, Brown EN: Methylphenidate actively induces emergence from general anesthesia. Anesthesiology 2011; 115:791–803
4. Taylor NE, Chemali JJ, Brown EN, Solt K: Activation of D1 dopamine receptors induces emergence from isoflurane general anesthesia. Anesthesiology 2013; 118:30–9
5. Lu J, Jhou TC, Saper CB: Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. J Neurosci 2006; 26:193–202
6. Franks NP: General anaesthesia: From molecular targets to neuronal pathways of sleep and arousal. Nat Rev Neurosci 2008; 9:370–86
7. Nakayama M, Kanaya N, Ichinose H, Yamamoto S, Namiki A: Intravenous droperidol causes a reduction in the bispectral index in propofol-sedated patients during spinal anesthesia. Anesth Analg 2003; 96:765–8
8. Adachi YU, Tanaka K, Suzuki S, Nishiwaki K, Matsuda N: Intravenous droperidol decreases the bispectral index during general anesthesia with sevoflurane and remifentanil. Masui 2013; 62:71–4
9. Ford CP: The role of D2-autoreceptors in regulating dopamine neuron activity and transmission. Neuroscience 2014; 282:13–22
10. Heyer EJ, Flood P: Droperidol suppresses spontaneous electrical activity in neurons cultured from ventral midbrain. Implications for neuroleptanesthesia. Brain Res 2000; 863:20–4
11. Grenhoff J, Johnson SW: Electrophysiological effects of dopamine receptor stimulation, The dopamine receptors. Edited by Neve KA, Neve RL. New York, Humana Press, 1997, pp 267–30
12. Buzsáki G: The brain's default state: Self-organized oscillations in rest and sleep, Rhythms of the brain. Edited by Buzsáki G. New York, Oxford University Press, 2006, pp 175–205
13. Vyazovskiy VV, Riedner BA, Cirelli C, Tononi G: Sleep homeostasis and cortical synchronization: II. A local field potential study of sleep slow waves in the rat. Sleep 2007; 30:1631–42
14. Ching S, Cimenser A, Purdon PL, Brown EN, Kopell NJ: Thalamocortical model for a propofol-induced alpha-rhythm associated with loss of consciousness. Proc Natl Acad Sci U S A 2010; 107:22665–70
15. Feige B, Scheffler K, Esposito F, Di Salle F, Hennig J, Seifritz E: Cortical and subcortical correlates of electroencephalographic alpha rhythm modulation. J Neurophysiol 2005; 93:2864–72
16. Schneider G, Kochs EF: The search for structures and mechanisms controlling anesthesia-induced unconsciousness. Anesthesiology 2007; 107:195–8
17. Hayashi K, Sawa T, Matsuura M: Anesthesia depth-dependent features of electroencephalographic bicoherence spectrum during sevoflurane anesthesia. Anesthesiology 2008; 108:841–50
18. Sigl JC, Chamoun NG: An introduction to bispectral analysis for the electroencephalogram. J Clin Monit 1994; 10:392–404
19. Hagihira S, Takashina M, Mori T, Mashimo T, Yoshiya I: Changes of electroencephalographic bicoherence during isoflurane anesthesia combined with epidural anesthesia. Anesthesiology 2002; 97:1409–15
20. Morimoto Y, Hagihira S, Yamashita S, Iida Y, Matsumoto M, Tsuruta S, Sakabe T: Changes in electroencephalographic bicoherence during sevoflurane anesthesia combined with intravenous fentanyl. Anesth Analg 2006; 103:641–5
21. Hayashi K, Mita K, Sawa T: Electroencephalographic changes in the late cardiopulmonary bypass period are not reflected in the bispectral index. Clin Neurophysiol 2010; 121:1198–204
22. Hayashi K, Mukai N, Sawa T: Simultaneous bicoherence analysis of occipital and frontal electroencephalograms in awake and anesthetized subjects. Clin Neurophysiol 2014; 125:194–201
23. Hayashi K, Fujikawa M, Sawa T: Hyperventilation-induced hypocapnia changes the pattern of electroencephalographic bicoherence growth during sevoflurane anaesthesia. Br J Anaesth 2008; 101:666–72
24. Hagihira S: User manual for BSA Ver 3.31B (Bispectrum Analyzer for BIS). Available at: http://www.med.osaka-u.ac.jp/pub/anes/www/html/manual/Bsa_BIS/Bsa_BIS_e.html. Accessed October 2, 2004.
25. Alkire MT, Hudetz AG, Tononi G: Consciousness and anesthesia. Science 2008; 322:876–80
26. Purdon PL, Sampson A, Pavone KJ, Brown EN: Clinical electroencephalography for anesthesiologists: Part I: Background and basic signatures. Anesthesiology 2015; 123:937–60
27. Akeju O, Westover MB, Pavone KJ, Sampson AL, Hartnack KE, Brown EN, Purdon PL: Effects of sevoflurane and propofol on frontal electroencephalogram power and coherence. Anesthesiology 2014; 121:990–8
28. Gottschalk A, Miotke SA: Volatile anesthetic action in a computational model of the thalamic reticular nucleus. Anesthesiology 2009; 110:996–1010
29. Yasumoto F, Negishi T, Ishii Y, Kyuwa S, Kuroda Y, Yoshikawa Y: Endogenous dopamine maintains synchronous oscillation of intracellular calcium in primary cultured-mouse midbrain neurons. Cell Mol Neurobiol 2004; 24:51–61
30. España RA, Schmeichel BE, Berridge CW: Norepinephrine at the nexus of arousal, motivation and relapse. Brain Res 2016; 1641(part B):207–16
31. Berridge CW, Schmeichel BE, España RA: Noradrenergic modulation of wakefulness/arousal. Sleep Med Rev 2012; 16:187–97
32. Samuels ER, Szabadi E: Functional neuroanatomy of the noradrenergic locus coeruleus: its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. Curr Neuropharmacol 2008; 6:235–53
33. Pudovkina OL, Cremers TI, Westerink BH: Regulation of the release of serotonin in the dorsal raphe nucleus by alpha1 and alpha2 adrenoceptors. Synapse 2003; 50:77–82
34. Flood P, Coates KM: Droperidol inhibits GABA(A) and neuronal nicotinic receptor activation. Anesthesiology 2002; 96:987–93
35. Tritsch NX, Ding JB, Sabatini BL: Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. Nature 2012; 490:262–6
36. Hassan A, Benarroch EE: Heterogeneity of the midbrain dopamine system: Implications for Parkinson disease. Neurology 2015; 85:1795–805
37. Kenny JD, Chemali JJ, Cotten JF, Van Dort CJ, Kim SE, Ba D, Taylor NE, Brown EN, Solt K: Physostigmine and

methylphenidate induce distinct arousal states during isoflurane general anesthesia in rats. Anesth Analg 2016; 123:1210–9

38. Koos T, Tecuapetla F, Tepper JM: Glutamatergic signaling by midbrain dopaminergic neurons: Recent insights from optogenetic, molecular and behavioral studies. Curr Opin Neurobiol 2011; 21:393–401
39. Margolis EB, Lock H, Hjelmstad GO, Fields HL: The ventral tegmental area revisited: Is there an electrophysiological marker for dopaminergic neurons? J Physiol 2006; 577(part 3):907–24
40. Tanifuji Y, Zhang Y, Liao M, Eger EI 2nd, Laster MJ, Sonner JM: Do dopamine receptors mediate part of MAC? Anesth Analg 2006; 103:1177–81
41. Staikou C, Stamelos M, Stavroulakis E: Impact of anaesthetic drugs and adjuvants on ECG markers of torsadogenicity. Br J Anaesth 2014; 112:217–30
42. Satomoto M, Adachi YU, Makita K: A low dose of droperidol decreases the desflurane concentration needed during breast cancer surgery: A randomized double-blinded study. Korean J Anesthesiol 2017; 70:27–32