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The Midlatency Auditory Evoked Potentials Predict Responsiveness to Verbal Commands in Patients Emerging from Anesthesia with Xenon, Isoflurane, and Sevoflurane but Not with Nitrous Oxide

Takahisa Goto, M.D., Yoshinori Nakata, M.D., M.B.A.,* Hayato Saito, B.S.,† Yoshiki Ishiguro, M.D.,‡ Yoshinari Niimi, M.D., Ph.D.,* Shigeho Morita, M.D.§*

Background: **It has recently been demonstrated that the approximately 40-Hz spectral power of the midlatency auditory evoked potential (MLAEP) correlates well with wakefulness during desflurane or propofol anesthesia. The aim of this study was to characterize how other inhalational anesthetics affects the MLAEP as the patients regain responsiveness to simple verbal command during emergence from anesthesia.**

Methods: **Sixty patients were randomly assigned to receive xenon, isoflurane, sevoflurane, or nitrous oxide (N_2O) supplemented with epidural anesthesia. During emergence, the concentration of an anesthetic was decreased in 0.1-minimum alveolar concentration (MAC) decrements from 0.8 MAC or from 70% in the case of N_2O, and each new concentration was maintained for 15 min. Every 5 min during each equilibration period, the MLAEP was recorded and the patients were asked to open their eyes and squeeze and release the investigator's hand. This process was repeated until the first response to either of these commands was observed.**

Results: **Thirteen patients were excluded because of technical reasons. The preanesthetic MLAEP showed a periodic waveform, where the Na-Pa-Nb complex was the most prominent component contributing to the high energy around 29–39 Hz in the power spectrum. Emergence from xenon, isoflurane, and sevoflurane anesthesia produced similar changes in the MLAEP. The spectral power for the frequency 29 Hz or greater was severely suppressed at 0.8 MAC but significantly recovered between the concentration only 0.1 MAC higher that permitting the first response to command and that associated with the first response. In contrast, N_2O hardly affected the MLAEPs, even at the concentrations producing unresponsiveness. Two patients did not lose responsiveness even at the highest concentration tested (70%).**

Conclusions: **The MLAEP is closely associated with responsiveness to verbal command during emergence from anesthesia with xenon, isoflurane, and sevoflurane but not with N_2O.**

THE midlatency auditory evoked potentials (MLAEPs) are a series of cerebral electrical activities elicited 10–100 ms after acoustic stimulation, *i.e.*, immediately after the brainstem auditory evoked potentials.[1] Accumulating evidence suggests that the MLAEPs may predict wakefulness during anesthesia, defined as the presence of response to simple verbal command.[2–4] More recently, it has been demonstrated that the spectral power of the MLAEP at the frequency of approximately 40 Hz predicts wakefulness better than amplitudes and latencies of various peaks during desflurane or propofol anesthesia.[5]

Not all anesthetics affect the MLAEP in a similar fashion, however. For example, nitrous oxide (N_2O) is distinctly less effective than isoflurane in attenuating the MLAEPs.[6] Furthermore, although volatile anesthetics are qualitatively similar in their concentration–MLAEP effect relation,[7–9] some quantitative differences may exist.[10] Consequently, it remains unclear if the close correlation between the activity of the MLAEP at approximately 40 Hz and the level of consciousness demonstrated for desflurane and propofol holds true for other inhalational anesthetics. To elucidate this point, we sought to characterize how the MLAEP, especially its activity at the frequency around 40 Hz, changed as the patient emerged from anesthesia with various inhalational anesthetics. We chose two modern volatile anesthetics, isoflurane and sevoflurane, both similar to desflurane with respect to their molecular structures, and two gaseous anesthetics, N_2O and xenon, both totally unrelated to it. In particular, we predicted that xenon would have little effects on the MLAEP based on its putative mechanisms of action: xenon has no action on the γ-aminobutyric $acid_A$ ($GABA_A$) receptors,[11] whereas volatile anesthetics potentiate their function. Furthermore, xenon inhibits the function of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptors[11] like ketamine, which hardly affects the MLAEP even at anesthetizing doses.[12]

Methods and Materials

This study was conducted simultaneously with our investigation to determine the minimum alveolar concentration (MAC)-awake of anesthetics[13]; therefore, the criteria for the patient selection and anesthesia protocols were identical and are described only briefly here. This study was approved by the Institutional Human Studies Committee of Teikyo University.

* Associate Professor, ‡ Assistant Professor, § Professor and Chairman, Department of Anesthesia, † Chief Medical Engineer, Department of Medical Engineering.

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Address reprint requests to Dr. Goto: Department of Anesthesia, Teikyo University Ichihara Hospital, 3426-3 Anesaki, Ichihara-shi, Chiba 299-0111, Japan. Address electronic mail to: takigoto@med.teikyo-u.ac.jp.

Table 1. Patient Demographics, Postoperative Data, and MAC_{awake}

	Xenon	Isoflurane	Sevoflurane	N_2O
Age (yr)	46 ± 8	43 ± 8	47 ± 9	47 ± 8
Height (cm)	155 ± 6	157 ± 5	156 ± 3	154 ± 5
Weight (kg)	56 ± 7	59 ± 7	59 ± 11	55 ± 7
Duration of anesthesia (min)	115 ± 39	148 ± 59	119 ± 30	130 ± 49
Esophageal temperature (°C)	36.0 ± 0.1	35.9 ± 0.2	35.9 ± 0.1	35.9 ± 0.1
Epidural dose (ml)	31 ± 9	30 ± 7	27 ± 6	31 ± 9
Epidural level	T8 (T6–T11)	T8 (T4–T11)	T8 (T4–T10)	T8 (T4–T10)
Pain rating	2 (0–5)	2 (0–5)	2 (0–5)	2 (0–4)
MAC_{awake} (%)	30.9 ± 4.7	0.40 ± 0.07	0.58 ± 0.10	64.1 ± 8.3

Esophageal temperature was measured at the time of the first responsiveness to a verbal command. Epidural dose is the total volume of 1.5% mepivacaine with 1:200,000 epinephrine administered epidurally until 15 min after extubation. Epidural level was checked using pin pricks 15 min after extubation. The pain rating was the numerical quantification of incisional pain by the patient using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively. Data are mean ± SD, except for the epidural level and the pain rating, which are reported as median (range).

Participants and Anesthesia Protocols

After written informed consent was obtained, 60 women with American Society of Anesthesiologists physical status I or II, who were aged 32–64 yr and were scheduled for elective total abdominal or vaginal hysterectomy, were randomly assigned to receive xenon, isoflurane, sevoflurane, or N_2O (n = 15/group). No premedication was given. After induction using propofol or sevoflurane and tracheal intubation, anesthesia was maintained using 56% xenon, 1.0–1.5% isoflurane, 1.2–2.5% sevoflurane, or 70% N_2O as assigned (the MAC of xenon is 71%[14]; all concentrations of inhalational anesthetics are end tidal unless otherwise specified). The patients who received N_2O received approximately 0.5% of supplemental sevoflurane to prevent intraoperative awareness.[15] All patients also received a continuous infusion of 1.5% mepivacaine containing 1:200,000 epinephrine at 6–8 ml/h *via* an epidural catheter placed at the L2–L3 interspace so that the mean arterial pressure and heart rate were maintained within 20% of the preoperative values.

For at least 15 min before the anticipated end of surgery, the concentrations of isoflurane, sevoflurane, and xenon were maintained at 0.92%, 1.4%, and 56%, respectively (each corresponding to approximately 0.8 times the age-adjusted MAC[16]). In the N_2O group, sevoflurane was discontinued 30 min before the end of surgery and was washed out using a 10-l/min fresh flow of 70% N_2O in oxygen so that no more than 0.01% end-tidal concentration of sevoflurane was detected during the last 10 min.

Shortly before the end of surgery, residual neuromuscular blockade was reversed with 2.5 mg neostigmine and 1.0 mg atropine administered intravenously. When the surgery was completed, an investigator blinded to the anesthetic agent and concentration administered recorded the MLAEP. Then another investigator blinded to the MLAEP and the anesthetic administered asked the patient in a normal tone to open her eyes and then to squeeze and release the investigator's hand. If the patient did not follow either of these commands, the end-tidal concentration of an anesthetic was reduced by the primary anesthetist in a decrement of approximately 0.1 MAC (0.12% for isoflurane, 0.2% for sevoflurane, 7% for xenon, and 10% for N_2O), and the new concentration was maintained for 15 min. During this period, an MLAEP was recorded three times (*i.e.*, every 5 min), each immediately followed by a testing for responsiveness to verbal commands. This process was repeated until an alveolar concentration was reached at which the patient first responded to either one of the commands (eye opening or hand squeezing and releasing). If the patient showed clinical signs of impending emergence such as spontaneous movements or coughs, responsiveness to verbal command was checked immediately. If the patient responded, the anesthetic was discontinued and the patient was allowed to awaken without recording the MLAEP. If the patient was unresponsive, she was left undisturbed until these clinical signs disappeared, and then an MLAEP was recorded. Mechanical ventilation was continued during the entire period. When coughing or bucking hindered effective ventilation with positive pressures, the ventilator was stopped to avoid excessive elevations in the airway pressure. Fifteen minutes after extubation, the epidural block level to pin pricks was examined, and the patient was asked to rate her incisional pain using a 0–10 verbal rating scale, with 0 and 10 being no pain and the worst pain imaginable, respectively.

Recording of the Auditory Evoked Potentials

The MLAEPs were recorded preoperatively on the day of the operation while the patient was awake on the ward and during emergence from anesthesia as stated previously. The electrodiagnostic system (Neuropack 2; Nihon-Koden, Tokyo, Japan) was used. Rarefaction clicks of 0.1 ms at 80 dB absolute were presented binaurally with a stimulation frequency of 5 Hz using earphones applied only during the MLAEP recordings (*i.e.*, not during the subsequent testing of responsiveness to verbal commands). For recording, silver-silver chloride

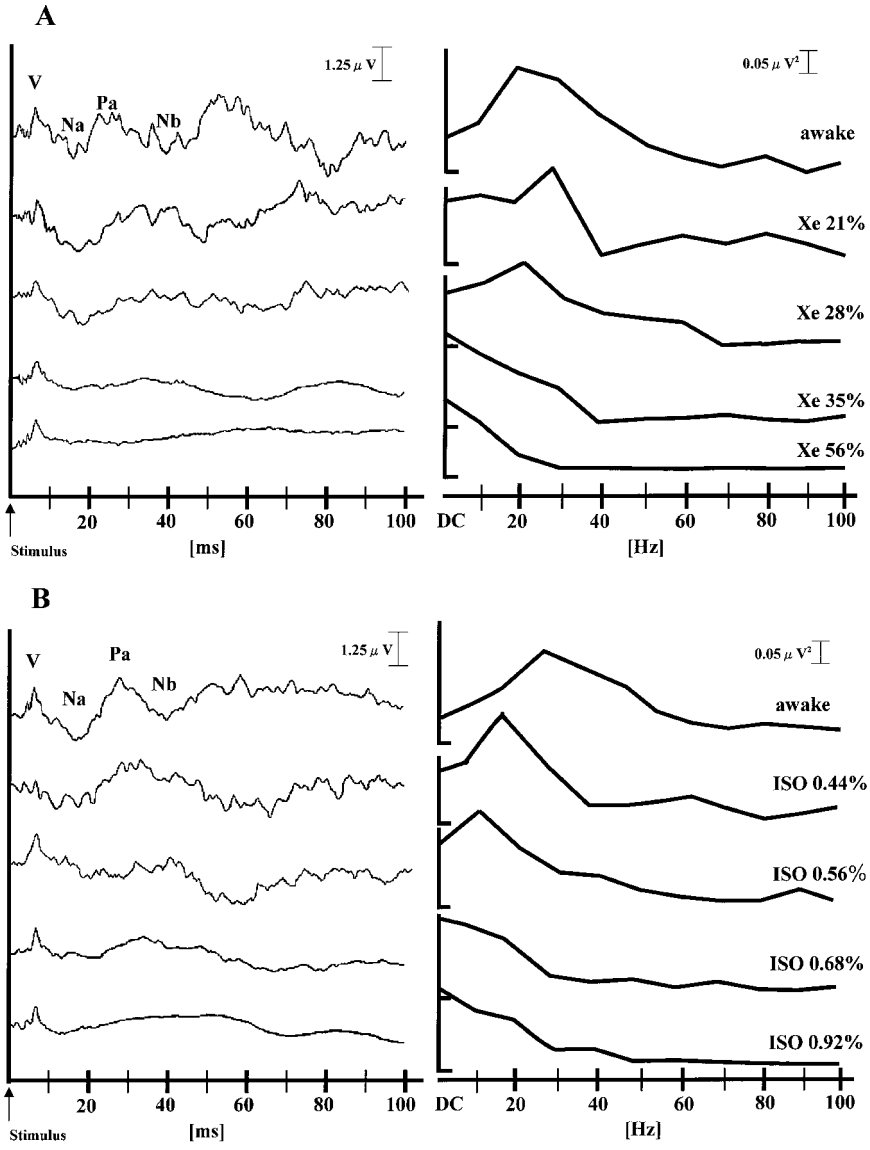

Fig. 1. (continued on next page) The representative midlatency auditory evoked potential tracings (*left*) and their power spectra (*right*) of the patients who received xenon (Xe; *A*), isoflurane (ISO; *B*), sevoflurane (SEVO; *C*), and nitrous oxide (N_2O; *D*). In each figure, the auditory evoked potential tracings represent (from top to bottom) preinduction awake, the awakening concentration, the 0.1-MAC-higher concentration, and (for figs. 1A–C) the 0.2-MAC-higher and 0.8 MAC concentrations. The short horizontal bars on the left side of the power spectra represent 0 power level. In each auditory evoked potential tracing, the wave of the first 10 ms consists of the brainstem response, where V is the most prominent peak, whereas the later component (10–100 ms) corresponds to the midlatency auditory evoked potential tracing. In the preinduction awake state, a typical periodic waveform with three distinct peaks—Na, Pa, and Nb—was observed.

electrodes were positioned at Cz (positive) and A1/A2 (negative) with Fpz as ground according to the international 10-20 system. The impedance of all electrodes was less than 5.0 kΩ. An epoch of 100 ms was acquired at the AD conversion rate of 5 KHz, bandpass-filtered (5–1,000 Hz), and averaged across 500 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artifact detector rejected signals greater than 5.0 μV. The waveforms were stored on floppy disks for later offline analyses.

Data Presentation and Statistical Analysis

The MAC_{awake} of an anesthetic was calculated for each patient as the mean of the concentrations permitting and just preventing the first response to command.[17] Because two patients in the N_2O group responded to verbal command at the highest concentration tested (70%), the MAC_{awake} of N_2O was calculated as in a previous study[18] by assuming that these patients would not have responded at 80%.[19]

Regarding the MLAEP, the latencies to the peaks Na, Pa, and Nb from the time of the auditory stimulation were measured. In addition, a fast-Fourier transformation was used to calculate the power spectra of the MLAEPs (MAC-Lab, ver. 3.5.4/s; AD Instruments, Mountain View, CA) as in previous studies by Schwender *et al.*[20] and Dutton *et al.*[5] Because a 100-ms MLAEP waveform acquired by our Neuropack 2 system consisted of 500 data points, zero padding was added to extend the epoch to 102.4 ms (512 data points). Therefore, the frequency resolution of our fast-Fourier transformation power spectra was 9.8 (= 5,000/512) Hz, *i.e.*, the fast-Fourier transformation computed the power at 0 (DC), 10, 20, 29, 39, 49, 59, 68, 78 Hz and so on. At each frequency between 29 and 78 Hz, the powers of the isoflurane, sevoflurane, and xenon groups were compared using the two-factor

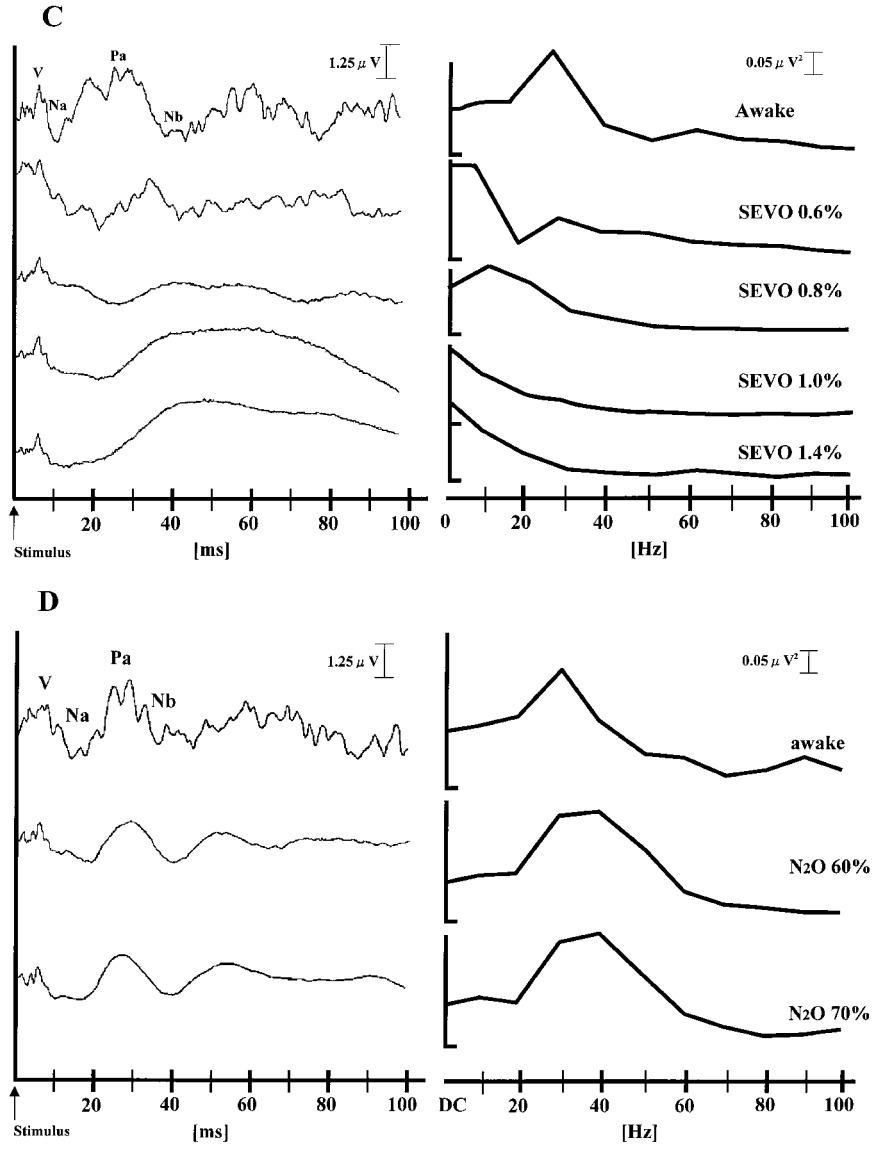

Fig. 1 Continued.

(anesthetic agent × anesthetic level) repeated-measures analysis of variance across the following five anesthetic concentrations: (1) the awake state before induction of anesthesia; (2) the concentration at which the patient first responded to the command (termed "the awakening concentration"); (3) one step (approximately 0.1 MAC) higher than (2) (the "0.1-MAC-higher" concentration); (4) two steps (approximately 0.2 MAC) higher than (2) (the "0.2-MAC-higher" concentration); and (5) 0.8 MAC (0.92, 1.4, and 56% for isoflurane, sevoflurane, and xenon, respectively).

Post hoc analyses were performed using the Student-Newman-Keuls test. The latencies of peaks Na, Pa, and Nb were analyzed similarly, except that the data at 0.8 MAC were not included in the analyses. This was because in approximately half of the patients who received isoflurane or sevoflurane, the MLAEP waveforms at 0.8 MAC were too flattened to allow identification of these peaks with acceptable precision.

The N_2O group was analyzed separately by comparing the data at the anesthetic concentrations (1) to (3) described above because the awakening concentrations in this group were high (60 or 70% in all but two patients), precluding data acquisition at the 0.2-MAC-higher (20%) concentration. The comparisons among these anesthetic concentrations were performed using three paired *t* tests [(1) *vs.* (2), (1) *vs.* (3), and (2) *vs.* (3)] for each MLAEP parameter to maximize the number of patients included in each analysis.

Results are reported as mean ± SD unless otherwise specified. Except for the auditory evoked potential parameters stated above, data were analyzed using single-factor factorial analysis of variance and the Student-Newman-Keuls test. The postoperative pain rating and the

epidural level were expressed as median (range) and were analyzed using the Kruskal–Wallis test because they are discrete numbers. Statistical significance was accepted at $P < 0.05$, except for the MLAEP data of the N_2O group, where $P < 0.0167$ (0.05/3) was used.

Results

Thirteen patients (three each in the xenon, isoflurane, and sevoflurane groups and four in the N_2O group) were excluded because of the following technical reasons: (1) persistent post-auricular muscle potentials distorting the MLAEP waveforms near the Na peak (n = 6)[21]; (2) excessive excitement during emergence precluding adequate recording of MLAEPs at both the awakening and the 0.1-MAC-higher concentrations (n = 3); (3) accidental loss of data from the disks (n = 4).

For the remaining 47 patients, the four anesthetic treatment groups were comparable with respect to patient demographics and other postoperative data listed in table 1. The MAC_{awake} values for isoflurane, sevoflurane, and N_2O were in good agreement with those reported by other investigators (table 1).[18,22]

Figures 1A–D show the representative MLAEP tracings and their power spectra. In the awake state, typical periodic waveforms with three distinct peaks—Na, Pa, and Nb—were observed. This Na-Pa-Nb complex contributed to the energy peak at approximately 30–40 Hz in the power spectrum because it was approximately 25–30 ms in duration. This complex is known to be the largest and most reproducible component of the MLAEP.[21]

The MLAEPs were affected little by N_2O, even at the 0.1-MAC-higher concentration, where the patient was unresponsive (the bottom tracing in fig. 1D). In contrast, the three other anesthetics produced very similar alterations in the MLAEPs (figs. 1A–C). The waveforms were markedly flattened at the 0.8-MAC (the bottom tracing in each figure) and the 0.2-MAC-higher concentrations (the second tracing from the bottom). At the awakening concentration, however, the three peaks Na, Pa, and Nb could be distinctly recognized, albeit somewhat prolonged in latency and smaller in amplitude than those in the awake state (the second tracing from the top). In agreement with this, the spectral power at each frequency 29 Hz or greater was markedly reduced at the 0.8-MAC and the 0.2-MAC-higher concentrations of anesthesia but was partially restored at the awakening concentration.

Figures 2A and 2B demonstrate the MLAEP spectral power plotted against the concentrations of anesthetics. Each data point involves 12 (xenon, isoflurane, and sevoflurane) or 11 (N_2O) patients. At the awakening concentration only, however, the data represent 10 xenon, 8 isoflurane, 6 sevoflurane, or 7 N_2O patients because the MLAEP could not be recorded at this concentration in the remaining patients (see Methods). The anesthetic concentrations were expressed in the multi-

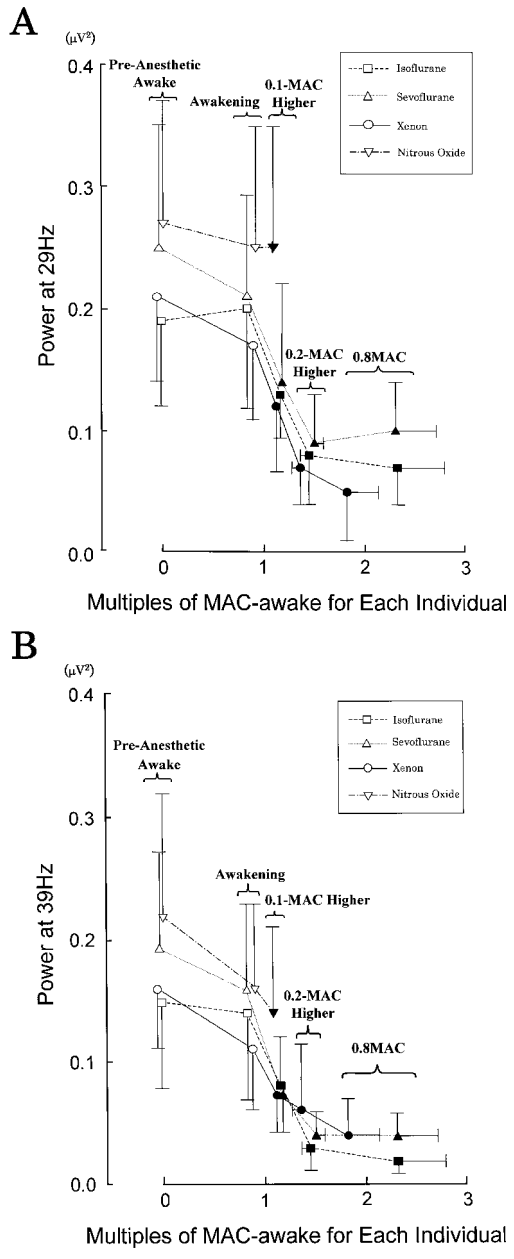

Fig. 2. The anesthetic-induced changes in the spectral power for the frequency of 29 Hz (*A*) and 39 Hz (*B*) in patients receiving xenon, isoflurane, sevoflurane, and nitrous oxide. On the horizontal axis, the concentrations of anesthetics were expressed as multiples of MAC_{awake}. These values were calculated by dividing the actual concentrations by the mean of the awakening and the 0.1-MAC-higher concentrations for each individual patient, which was by definition the MAC_{awake} of each individual. At the awakening concentration only, the data represent 10 of 12 xenon, 8 of 12 isoflurane, 6 of 12 sevoflurane, and 7 of 11 nitrous oxide patients because the midlatency auditory evoked potential could not be recorded at this concentration in the remaining patients. The open and closed symbols indicate the presence and the absence of responses to verbal command, respectively. Data are mean ± SD. See the text for the detailed results of statistical analyses.

Table 2. Latencies to the MLAEP Peaks

	Preinduction	Awakening	0.1 MAC Higher	0.2 MAC Higher	0.8 MAC
Na					
Xenon	17 ± 3	20 ± 2	19 ± 2	20 ± 3	23 ± 3 (9)
Sevoflurane	16 ± 3	21 ± 2	23 ± 3	25 ± 5	25 ± 3 (9)
Isoflurane	16 ± 2	20 ± 4	20 ± 4	23 ± 5	29 ± 7 (4)
N_2O	18 ± 2	18 ± 1	19 ± 3		
Pa					
Xenon	28 ± 5	34 ± 3	36 ± 4	35 ± 4	45 ± 8 (10)
Sevoflurane	29 ± 4	35 ± 6	40 ± 5	43 ± 7	43 ± 7 (9)
Isoflurane	28 ± 3	34 ± 5	36 ± 5	48 ± 7	47 ± 10 (5)
N_2O	31 ± 4	30 ± 3	33 ± 3		
Nb					
Xenon	44 ± 5	49 ± 5	57 ± 8	62 ± 14	71 ± 9 (8)
Sevoflurane	46 ± 4	50 ± 9	63 ± 12	68 ± 12	68 ± 10 (9)
Isoflurane	43 ± 4	50 ± 10	60 ± 9	72 ± 10	73 ± 9 (6)
N_2O	46 ± 4	47 ± 6	51 ± 5		

Data are mean ± SD (ms). The data at 0.8 MAC represent the numbers of the patients in parentheses. See text for the results of statistical analysis. MLAEP = midlatency auditory evoked potential; N_2O = nitrous oxide.

ples of the MAC_{awake} for each individual patient, *i.e.*, by dividing the actual concentration for each patient by the mean of the awakening and the 0.1-MAC-higher concentrations of that patient. This had dual purposes; first, to quantify the concentrations of anesthetics based on the clinical end point of interest in this study (responsiveness to verbal command); and second, to compensate for the variability in the sensitivity of individual patients to anesthetics.

Xenon, isoflurane, and sevoflurane similarly altered the MLAEP spectral power at each frequency between 29 and 78 Hz ($P < 0.005$ for anesthetic concentrations, NS for anesthetics and interaction, two-factor repeated-measures analysis of variance). Only the results at 29 and 39 Hz are presented in figures 2A and 2B because the data at the greater frequencies demonstrated comparable changes. At each frequency, the *post hoc* analyses performed by pooling the data of the three anesthetics revealed the following: (1) the power in the preinduction awake state was significantly greater than those at the 0.8-MAC, 0.2-MAC-higher, and 0.1-MAC-higher concentrations of anesthesia, but was not different from that at the awakening concentration; (2) the power at the awakening concentration was significantly greater than those at the 0.8-MAC, 0.2-MAC-higher, and 0.1-MAC-higher concentrations; (3) the power was not significantly different between the 0.2-MAC-higher and the 0.8 MAC concentrations.

Regarding the latency to the Nb peak, xenon, isoflurane, and sevoflurane again had similar effects (table 2). Furthermore, statistically significant differences were found for the same pairs of anesthetic concentrations as in the case of the MLAEP spectral power. The latencies to the Na and Pa peaks were also prolonged at deeper concentrations of anesthesia, although the changes were less marked than that of the Nb latency. Moreover, they were not consistent among xenon, isoflurane, and sevoflurane because the repeated-measures analysis of variance showed significant interactions between anesthetics and anesthetic concentrations.

Unlike these three anesthetics, N_2O had little effects on the MLAEP spectral power and latencies. The only significant differences detected were those in the spectral power between the preinduction and the 0.1-MAC-higher concentration at 39 ($P = 0.043$), 68 ($P = 0.017$) and 78 Hz ($P = 0.001$). Neither the spectral power at other frequencies nor the latencies to any of the peaks changed significantly (figs. 2A and 2B and table 2). Notably, there was no difference between the awakening concentration and the 0.1-MAC-higher concentration in any of the MLAEP parameters analyzed, although this might be because only five patients were included in this comparison. For the comparisons of preinduction *versus* the awakening concentration and preinduction *versus* the 0.1-MAC-higher concentration, seven and nine patients were analyzed, respectively.

Discussion

We demonstrated that xenon, isoflurane, and sevoflurane allowed similar and marked changes in the 29-Hz or greater spectral power of the MLAEP during emergence from anesthesia when their concentrations approached that associated with the first response to verbal command. Notably, the power significantly increased between the 0.1-MAC-higher and the awakening concentrations, *i.e.*, during the transition from unconsciousness to consciousness. Therefore, we conclude that the 29-Hz or greater spectral power of the MLAEP closely correlates with the presence–absence of response to simple verbal command during emergence from anesthesia with xenon, isoflurane, and sevoflurane.

This is consistent with the finding of Dutton *et al.*,[5] that the spectral power of the MLAEP at approximately 40 Hz predicts wakeful response during desflurane or

propofol anesthesia. They further specified by calculating prediction probability that the frequency associated with the highest prediction value was 40–45 Hz for both desflurane and propofol. Our results are also consistent with those of earlier reports[2–4] in which indices other than the spectral power were used to describe the MLAEPs.

This close relation between the MLAEP and the responsiveness to verbal command indicates that there is tight correlation between the functional integrity of the MLAEP neural generators and the responsiveness to verbal command during anesthesia with volatile anesthetics and xenon (and propofol[4,5]). The MLAEP is generated as the auditory signals transmit through the primary auditory cortex, perhaps with some additional contribution from the mesencephalic structures such as the medial geniculate.[1,21] Because the primary auditory cortex processes incoming acoustic signals as simple sounds,[23] it is not surprising from the audiological standpoint that the patients with attenuated MLAEPs were unresponsive to verbal commands.

Clinically, responsiveness to verbal command is a commonly used index of the level of consciousness during anesthesia because the presence of response heralds impending return of the subject's ability to form memory, while its absence generally ensures amnesia.[24] Therefore, one can safely infer from our results that the MLAEP correlates with the level of consciousness. The neural generators of an MLAEP, however, do not mediate consciousness because their selective destruction merely results in impaired auditory sensitivity in wakeful patients (so-called cortical deafness).[25] Consequently, we regard our results as evidence that the functional state of the MLAEP generators, and that of other parts of the brain mediating consciousness, are closely associated during anesthesia with volatile anesthetics and xenon.

This line of reasoning naturally follows that anesthetics with different cerebral actions may not necessarily provide association between the MLAEP and consciousness. One example, which we demonstrated in this study, is N_2O, because it produced unresponsiveness to verbal command without substantially affecting the MLAEPs.

This discrepancy may, at least in part, be accounted for by their metabolic effects on the brain. N_2O exerts a highly region-specific effect on the cerebral metabolic rate, leaving the primary auditory cortex relatively unaffected.[26] In contrast, both isoflurane and sevoflurane potently suppress the metabolic activity of the whole brain, including the primary auditory cortex.[27,28] With regard to xenon, a recent study showed its relatively homogenous effects on the regional cerebral metabolic rate.[29] This indicates that xenon, like isoflurane and sevoflurane but unlike nitrous oxide, anesthetizes the primary auditory cortex as well as other parts of the brain.

Contrary to our prediction, xenon was almost indistinguishable from isoflurane or sevoflurane with respect to their MLAEP effects. As far as we know, xenon is the first anesthetic without actions on the $GABA_A$ receptors[11] that has been demonstrated to attenuate the MLAEPs. All other anesthetics that suppress the MLAEPs, including volatile anesthetics, propofol,[5] thiopental,[30] and etomidate,[31] share $GABA_A$ agonistic properties. Therefore, our results provide the first evidence that activation–potentiation of the $GABA_A$ receptors is not the mandatory mechanism for attenuation of the MLAEPs by anesthetics. This is interesting in light of the fact that benzodiazepines have little effect on the MLAEPs, although they act specifically at the $GABA_A$ receptors and enhance their function.[32]

The inhibitory effects of xenon on the MLAEPs may appear odd with its putative mechanism of action (*i.e.*, it inhibits the function of the NMDA receptors[11]) because ketamine, a well-established antagonist of the NMDA receptor, has little effect on the MLAEPs.[12] However, evidence from the electroencephalographic studies indicates that anesthetizing concentrations of xenon slow the electroencephalogram,[33,34] while ketamine stimulates it.[35] Collectively, we argue that xenon and ketamine exert distinctly different electrophysiologic effects on the brain despite the fact that they share the NMDA receptor antagonistic properties.

Two additional findings not central to our study objective warrant discussion. First, among the latencies to the three peaks of the MLAEP (Na, Pa, and Nb), that to the Nb peak changed most consistently with the spectral power (table 2). This is in agreement with the previous reports demonstrating the efficacy of this index as a predictor of wakefulness.[2,3,5] Second, during xenon, isoflurane, and sevoflurane anesthesia, the 29-Hz or greater spectral power of the MLAEP was similarly and near-maximally suppressed at 0.8 MAC and at the concentration only 0.2 MAC higher than that associated with the first response to verbal command (the 0.2-MAC-higher concentration; figs. 2A and 2B). The latter concentration was, by definition, 0.15 MAC higher than the MAC_{awake} of each individual patient. Therefore, our finding implies that the concentration of an anesthetic exceeding the MAC_{awake} by only 0.15 MAC produces near-maximum suppression of the MLAEP and that further increases in the anesthetic concentration would add little to disruption of the neuronal activities mediating generation of the MLAEPs.

This study has several limitations. First, we changed the anesthetic concentrations in only one direction (decreased). However, there is evidence that the changes in MLAEPs are reproducible regardless of whether the patient is regaining or losing consciousness.[4] Second, we used epidural analgesia because of our wish to avoid systemic administration of supplemental analgesics. It is unknown whether epidural analgesia disturbs the rela-

tion between the MLAEPs and the responsiveness to verbal command. Third, our results for the awakening and the 0.1-MAC-higher concentrations of N_2O might have been confounded by the presence of residual sevoflurane used to supplement anesthesia during maintenance. Although we washed it out using a high flow of fresh gas, up to 0.05% (0.08 times MAC_{awake}) sevoflurane might have remained in the brain at the time of the MLAEP measurements.[36] Fourth, we could not examine whether N_2O was capable of suppressing the MLAEPs when administered at concentrations sufficiently higher than its MAC_{awake} because it was high (64%).

In summary, we demonstrated that the 29-Hz or greater spectral power of the MLAEPs closely correlated with the responsiveness to verbal command during anesthesia with isoflurane, sevoflurane, and xenon. In contrast, N_2O affected the MLAEP little, even in the absence of response to verbal command. Some other anesthetics such as ketamine[12] and benzodiazepines[32] are similar to N_2O in this respect. Although the MLAEP has been proposed as a useful clinical monitor of hypnosis during anesthesia,[24] this limitation should be borne in mind, especially when multiple drugs are used to produce anesthesia.

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