Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans†

G. PLOURDE, J. BARIBEAU AND V. BONHOMME

Summary
The auditory middle latency response (AMLR) and the 40-Hz auditory steady-state response (40-Hz ASSR) are evoked potentials which possibly arise from the same generators in the primary auditory cortex. Both responses are attenuated by most general anaesthetics. Ketamine, however, has been reported to have no effect on the AMLR. Our aim was to evaluate the effects of ketamine on the 40-Hz ASSR. Spectral analysis of the electroencephalogram (EEG) was also conducted to independently examine the effects of ketamine. Ketamine 1.5 mg kg$^{-1}$ was given to 12 patients for induction of general anaesthesia. Recordings of the 40-Hz ASSR and EEG were obtained every minute from 3 min before administration of ketamine to 5 min after injection, when the study was terminated. Similar recordings were obtained in three control subjects under identical conditions except that no medication was administered. Consciousness, defined as responsiveness to verbal commands, was assessed before each recording. Ketamine caused an increase in the amplitude of the 40-Hz ASSR ($P<0.01$). Using published AMLR data, we conducted a simulation experiment that suggested that the effect of ketamine on the AMLR can explain its effects on the amplitude of the 40-Hz ASSR. There was a pronounced increase in relative theta (3.9–7.9 Hz) EEG power and a decrease in relative alpha (8.0–12.8 Hz) power ($P<0.001$). These changes were not observed in the control group. Ketamine produced unconsciousness until the end of the study in five patients and transient unconsciousness in five patients. Two patients did not lose consciousness after administration of ketamine. The 40-Hz ASSR and EEG revealed no consistent differences between conscious and unconscious patients. No relationship could be demonstrated between the increase in amplitude of the 40-Hz ASSR or of relative theta power (the hallmark of ketamine effect) and loss of responsiveness to commands. We conclude that ketamine, unlike other anaesthetics, increases the amplitude of the 40-Hz ASSR. (Br. J. Anaesth. 1997; 78: 524–529).

Key words

The auditory middle-latency response (AMLR)$^1$ and the 40-Hz auditory steady-state response (40-Hz ASSR)$^2$ are affected by general anaesthetics. Both responses are auditory evoked potentials, that is changes in the electrical activity of the brain caused by auditory stimuli. The AMLR and the 40-Hz ASSR probably arise from the same generator in the primary auditory cortex.$^3$ Differences between the two responses depend on the rate of stimulus delivery. The AMLR is a transient evoked response. Transient responses are evoked by stimuli presented at a rate sufficiently slow so that the response to one stimulus is over before the next stimulus occurs. The 40-Hz ASSR is a steady-state response. Steady-state responses are evoked by stimuli presented so rapidly as to cause overlapping of the responses to successive stimuli.$^4$

Schwender and colleagues$^5$ recently examined the effect of ketamine 2 mg kg$^{-1}$ on the AMLR during induction of general anaesthesia. They concluded that ketamine had no effect on the AMLR. The effects of ketamine on the 40-Hz ASSR have not been studied. The aim of this study was to measure the effect of ketamine 1.5 mg kg$^{-1}$ on the 40-Hz ASSR. It was not possible to concurrently record the AMLR but the EEG was recorded to document independently the effects of ketamine.

Patients and methods
The study was approved by the institutional Ethics Committee. We studied 12 ASA I elective surgical patients, aged 18–50 yr (mean 33 yr), who gave written informed consent. All were within the ideal body weight range (Metropolitan Weight Tables, 1983), denied past neurological or otological disease and had normal otoscopy. No premedication was given. After insertion of an i.v. cannula into the left arm and placement of monitors (ECG, arterial pressure cuff and pulse oximetry probe) patients breathed oxygen by face mask for 3 min. Three
baseline recordings of the 40-Hz ASSR were obtained, one every minute. Ketamine (Ketalar) 1.5 mg kg\(^{-1}\) was given over 15 s and the 40-Hz ASSR recorded every 1 min for 5 min, starting with the beginning of injection. Before each recording the level of consciousness was assessed by asking the patient to squeeze the fingers of an observer unaware of the 40-Hz ASSR results. A patient who obeyed was considered conscious.

At 5 min after administration of ketamine, the study was terminated. Midazolam 0.1 mg kg\(^{-1}\) and thiopentone 3 mg kg\(^{-1}\) were given before proceeding with standard anaesthetic care. While in the recovery room after surgery, patients were asked to describe what they remembered from the induction period.

To verify the stability of the responses, recordings were obtained in three volunteers (aged 30–40 yr) under identical conditions except that the i.v. cannula was only taped to the skin, rather than inserted into a vein, and no medication was administered.

A microcomputer (Intel 80386 processor) was used for controlling stimulus delivery and recording the electroencephalogram (EEG). Stimuli were 500 Hz tonebursts (10 ms duration; 2 ms rise and fall time; 84 dB peak equivalent sound pressure level) delivered binaurally at a rate of 40 s\(^{-1}\) via insert earphones (“E-A-R TONE” 3A, Cabot Corporation, Indianapolis, IN, USA). The stimulus waveform (gated continuous sine wave) was created by the microcomputer, fed through a digital-to-analogue (D/A) converter (D/A rate 20 kHz) and attenuated before reaching the earphones to obtain 84 dB.

The EEG was recorded from Cz\(^{6}\) with gold-plated cup electrodes filled with conductive gel. The reference was the right mastoid and the ground was on the back of the neck over the fifth cervical vertebra. Impedances were maintained at less than 3 k\(\Omega\) (at 30 Hz). The EEG was amplified (amplifier model 12A5, Grass Instruments Co., Quincy, MA, USA) with a bandpass of 0.3–100 Hz. The analogue-to-digital (A/D) sampling rate was 298.978 Hz with 12A5, Grass Instruments Co., Quincy, MA, USA) with a bandpass of 0.3–100 Hz. The analogue-to-digital (A/D) resolution was 12 bits. Epochs contaminated by excessive artefacts were rejected. The criterion for rejection was 10% or more data points exceeding +100 \(\mu\)V. Epochs were averaged by groups of 10.

MEASUREMENTS

40-Hz ASSR

Amplitude (baseline to peak) and phase (sine function) at 40 Hz were obtained by computing the fast Fourier transform (FFT)\(^{7}\) of the averaged waveforms. No windowing was used because the choice of the sampling frequency ensured that there would be an FFT term exactly at 40 Hz.

EEG

Because averaging uniformly attenuates all frequencies, it is possible to obtain an estimate of the power spectrum of the EEG from the averaged waveforms.\(^{8}\) The presence of evoked activity (40-Hz ASSR) does not interfere with this process, because it is outside the frequency range used for EEG analysis.\(^{8}\) Power from 30.0 to 38.0 Hz and from 42.0 to 50 Hz was first measured to estimate absolute gamma band power. The 38.0–42.0 Hz range was omitted to avoid contamination by the 40-Hz ASSR. A non-phase shift FFT-based digital filter\(^{7}\) was used to remove residual noise below 1.5 Hz and above 30 Hz. The power spectrum of the averaged waveforms was computed with FFT with a Hanning window. Absolute power in the following frequency bands was measured: delta (1.5–3.8 Hz), theta (3.9–7.9 Hz), alpha (8.0–12.8 Hz), beta 1 (12.9–19.9 Hz) beta 2 (20.0–30.0 Hz) and gamma (30.0–38.0 Hz and 42.0–50 Hz). Relative power for each band was obtained by dividing absolute power by total power (1.5–30 Hz plus gamma band).

STATISTICAL ANALYSIS

When required, data were log transformed to meet the normality assumption (Lilliefors test).\(^{9}\) Analysis of variance (ANOVA) for repeated measures with six levels (baseline, the average of the three baseline recordings and the 0-, 1-, 2-, 3- and 4-min recordings) was used. The least significant difference (LSD) test was used for planned post hoc comparison (baseline vs each subsequent recording).\(^{10}\) The Pearson product moment correlation coefficient\(^{11}\) was used to evaluate the relationships between variables at each assessment time. The Lilliefors test was carried out with the program Systat (version 5.2.1 for Macintosh) (SPSS Inc, Chicago, IL, USA). All other procedures were carried out with CSS Statistica (version 3.1 for DOS) (Statsoft Inc, Tulsa, OK, USA). The criterion for significance was \(P<0.01\). All differences approaching significance (0.01 < \(P<0.05\)) are indicated.

PREDICTING THE EFFECTS OF KETAMINE ON THE 40-HZ ASSR FROM ITS EFFECTS ON THE AMLR

It is reasonable to assume that in awake subjects the 40-Hz ASSR can be predicted from the AMLR by superposition.\(^{12,13}\) It was not possible to concurrently record the AMLR. The effects of ketamine 2 mg kg\(^{-1}\) on the AMLR have been described by Schwender and colleagues.\(^{3}\) Although these authors found no change in the amplitude and latencies of the peaks of the AMLR, inspection of their waveforms suggests that ketamine enhanced near 40-Hz oscillations occurring 40–80 ms after the stimulus. We have used the data of Schwender and colleagues\(^{5}\) to study the effect of ketamine on the amplitude of the 40-Hz ASSR.

Figures 1 and 2 from Schwender and colleagues\(^{5}\) were digitized with a flat-bed high resolution (600 dpi) scanner. The resulting bitmap images were traced manually with Corel Draw (version 2.0, Corel Draw Corporation, Ottawa, Canada). Each traced waveform was exported as a HPGL (Hewlett-Packard graphics language) file.\(^{15}\) The HPGL file contains the X-Y coordinates of the waveform. Cubic spline interpolation\(^{7}\) was used to obtain measurements from 0 to 99 ms in 1-ms steps. Visual...
inspection showed that the recovered waveforms were virtually identical to the originals from the article by Schwender and colleagues. The predicted 40-Hz ASSR waveform was computed from the recovered AMLR by summation of the four 25-ms segments of the AMLR (0–24, 25–49, 50–74 and 75–99 ms) (See Plourde and Villemure for a complete description of the computation.) The amplitude of the predicted ASSR was obtained by FFT.

Results

40-Hz ASSR

There was a decrease in amplitude for the recording started concurrently with administration of ketamine \((t=0\text{ min}, P<0.05)\) followed by a progressive increase in amplitude \((P<0.01 \text{ at } t=3\text{ min})\) (table 1, fig. 1). For phase, there was a sudden increase for the recording started 1 min after administration \((P<0.001)\). Phase remained significantly higher than baseline afterwards, despite a progressive decline towards baseline values (table 1, fig. 1). The control subjects showed no amplitude or phase changes with time.

EEG

Three variables showed significant changes after administration of ketamine: relative power in the alpha, beta 1 and theta frequency bands (table 1, fig. 2). There was a significant \((P<0.001)\) decrease in relative alpha power for the recording started 3 min after injection. Relative beta 1 power also decreased significantly \((P<0.01)\) from 1 min onwards after injection. There was a very pronounced and highly significant \((P<0.001)\) increase in relative theta power after injection. Relative alpha and theta power remained stable over time in the three control subjects. Relative beta 1 power however decreased by approximately 30% in the controls (compared with approximately 50% in patients).

There was a modest decrease in relative delta power after ketamine but the difference was not significant \((P=0.18, \text{ANOVA})\). Relative power in beta 2 and gamma bands remained stable over time in patients and control subjects (fig. 2).

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<tr>
<th>Table 1</th>
<th>Outcome of statistical analysis. I = Increase, D = decrease. *P &lt; 0.05, **P &lt; 0.01, ***P &lt; 0.001</th>
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Planned comparison: baseline vs recording started at
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RESPONSIVENESS TO VERBAL COMMANDS

Responsiveness to verbal commands was assessed before each recording. All patients were responsive for the baseline recordings and for recording during which ketamine was administered. Five patients became unresponsive for the four recordings started after administration of ketamine. Two patients remained responsive for all recordings after injection. Five patients remained responsive for one or two of the four recordings after injection. There were no differences between the five patients who remained unresponsive during all recordings after injection and two patients who remained responsive throughout, with regard to amplitude (fig. 3) and phase of the 40-Hz ASSR or to any EEG variables. Even during unresponsiveness to commands, patients’ eyes frequently remained intermittently open and the eyelash reflex to touch was present. No patient had any recollection of events after administration of ketamine.

PREDICTED 40-HZ ASSR FROM THE AMLR DATA OF SCHWENDER AND COLLEAGUES

The amplitude of the predicted 40-Hz ASSR is shown in table 2. The 40-Hz ASSR predicted from the grand average waveforms from Schwender and colleagues (their fig. 2, based on 20 patients) was
increased by 25–50% for up to 6 min after ketamine.
An increase in the amplitude of the predicted 40-Hz ASSR was also noted on the recordings obtained 0–2 min after ketamine for all four patients shown in figure 2 of Schwender and colleagues.5 A comparable increase was also noted with two of the four patients on the recordings obtained 2–4 min and 4–6 min after ketamine.

Discussion

Unlike other anaesthetics,17 ketamine increased the amplitude of the 40-Hz ASSR. This observation, though somewhat surprising, was not completely unexpected. The recordings of Schwender and colleagues5 raised the possibility that ketamine could have a facilitatory role on 40 Hz oscillations after auditory stimuli (see their fig. 2 which shows a new wave occurring 50–70 ms after the stimulus on the recording performed 4–6 min after administration of ketamine). Domino, Chodoff and Corsen18 observed increased amplitude of the middle latency somatosensory response evoked by electrical

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stimulation of the median nerve. Schultz and colleagues\textsuperscript{19} and Schwartz, Virden and Scott\textsuperscript{20} showed that ketamine increased spontaneous EEG activity in the 25–45 Hz range. Spontaneous fast (30–40 Hz) rhythms have been recorded during anaesthesia with ketamine and xylazine (an \(\alpha_2\) agonist for veterinary use) in thalamocortical networks of cats\textsuperscript{21} and in the hippocampus of rats.\textsuperscript{22}

Simulation of the 40-Hz ASSR using the data of Schwender and colleagues\textsuperscript{5} suggested that the effect of ketamine on the AMLR can explain its effect on the amplitude of the 40-Hz ASSR. The demonstration was particularly convincing for the grand average data from Schwender and colleagues\textsuperscript{5} (table 2). An increase in the amplitude of the predicted 40-Hz ASSR was also noted with the four individual subjects from Schwender and colleagues\textsuperscript{5} for the recording obtained 0–2 min after administration of ketamine. In two subjects, the increase in amplitude persisted until the last recording, obtained 4–6 min after ketamine. With simulation experiments, we place more emphasis on grand average rather than individual data, because the prediction process works best when there is minimal residual noise. We must acknowledge, however, that the time course of the increase in amplitude of the 40-Hz ASSR observed in this study occurred later than that predicted by the grand average data from Schwender and colleagues.\textsuperscript{5} The most likely explanation is the difference in the dose of ketamine between the two studies.

Another possible explanation for the increased 40-Hz ASSR amplitude after ketamine is to view the auditory system as a tuned oscillator\textsuperscript{12} with an optimal resonance frequency of 37–38 Hz\textsuperscript{23} and to propose that ketamine brings this optimal frequency closer to 40 Hz without changing the AMLR. At present we see no need for this explanation because our reconstruction experiment strongly suggested that the increased 40-Hz ASSR amplitude after ketamine can be explained by superposition of the AMLR.

We did not observe an increase in relative EEG gamma power, as anticipated from the observations of Schultz and colleagues\textsuperscript{19} and Schwartz, Virden and Scott.\textsuperscript{20} There are two possible explanations. We administrated a smaller dose of ketamine (1.5 mg kg\textsuperscript{-1}) than Schultz and colleagues (2–3 mg kg\textsuperscript{-1}) and Schwartz, Virden and Scott (2 mg kg\textsuperscript{-1}). We used averaged EEG traces (based on 10 epochs) for estimation of relative power. Transient modest increases in gamma activity during 2 or 3 epochs would probably be missed by using averages. However, we do not believe that exclusion of the 38–42 Hz range, which contained the 40-Hz ASSR, can explain the absence of the increase in gamma power.

In common with previous investigators, we observed a marked increase in theta power, the hallmark of the EEG effects of ketamine,\textsuperscript{18–20} and a decrease in alpha power.\textsuperscript{24} The beta 1 power band had not been specifically examined before. We noted a 50% decrease in beta 1 power after ketamine but the three control subjects showed a decrease of 30%. Further observations are required to clarify the effect of ketamine on beta 1 power. This question could perhaps have been resolved if we had studied a larger control group. Our primary motive for testing control subjects was, however, to exclude the remote possibility that the amplitude of the 40-Hz ASSR increases with repeated testing. Because a first group of three control subjects revealed no evidence of amplitude increase with time, we felt that these results were sufficient to confirm the stability of the 40-Hz ASSR and that no further testing with control subjects was required.

A surprising finding was that the above changes of the 40-Hz ASSR and of the EEG were the same whether or not patients remained conscious. This observation differs from the report of Domino, Chodoff and Corssen\textsuperscript{18} who indicated that theta activity was present only during unconsciousness, being replaced by fast activity on return of consciousness. Domino, Chodoff and Corssen\textsuperscript{18} defined consciousness as the ability to answer questions, a task more complex than following a simple command. The discrepancy between the observations of Domino, Chodoff and Corssen\textsuperscript{18} and our own could be explained by the difference in how consciousness was assessed.

Finally, consideration must be given to how ketamine increases the amplitude of the 40-Hz ASSR and spontaneous gamma rhythms. Ketamine is considered a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor.\textsuperscript{25,26} There is insufficient knowledge of the neurotransmitters involved in generation of the 40-Hz ASSR and spontaneous gamma rhythms to understand why antagonism of the NMDA receptor would enhance these rhythms. Our observations suggest however that the 40-Hz ASSR probably does not depend on NMDA receptors.

We conclude that ketamine, unlike other anaesthetics, increased the amplitude of the 40-Hz ASSR and that this effect can probably be explained by subtle alterations of the AMLR by ketamine.

**Acknowledgements**

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**References**


Ketamine, 40-Hz ASSR and EEG


