MID-LATENCY AUDITORY EVOKED POTENTIALS DURING KETAMINE ANAESTHESIA IN HUMANS

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SUMMARY

We studied mid-latency auditory evoked potentials (MLAEP) during induction of general anaesthesia with ketamine 2 mg kg\(^{-1}\). MLAEP were recorded before, during and after induction of general anaesthesia on the vertex (positive) and mastoid (negative) positions. Latencies of the peak V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 were measured. Fast-Fourier transformation was used to calculate power spectra of the MLAEP.

In the awake state, MLAEP had large peak-to-peak amplitudes and a periodic waveform. Peak latencies remained within the normal range. Power spectra indicated high energy in the 30–40 Hz frequency range. After induction of general anaesthesia with ketamine, there was no change in latency of peaks V, Na, Pa, Nb, P1 and no apparent reduction in amplitudes Na/Pa, Pa/Nb and Nb/P1. In the power spectra, frequencies in the range of 30–40 Hz retained high energy. Amplitudes and latencies of MLAEP did not change during induction of general anaesthesia with ketamine. Primary processing of auditory stimuli in the primary auditory cortex seemed to be preserved under ketamine. Suppression of sensory (auditory) information processing must take place at a higher cortical level in a dissociative manner. (Br. J. Anaesth. 1993; 71: 629–632)

KEY WORDS

Anaesthesia, general: ketamine, auditory evoked potential.

In an accompanying paper, we have described the use of mid-latency peaks of the auditory evoked potential (MLAEP) to assess depth of anaesthesia with opioids, and reviewed the data with volatile anaesthetic agents [1]. The anaesthetic state under ketamine differs from that produced by volatile anaesthetic agents [2]. Dreams and hallucinations are well known phenomena associated with ketamine [3] and may be related to insufficient suppression of sensory stimulus processing. The effect of ketamine on MLAEP, indicating primary cortical processing of auditory stimuli, has not been studied. Therefore, we investigated changes in MLAEP during induction of general anaesthesia with ketamine.

RESULTS

Original tracings of AEP of four patients are shown in figure 1. Data are shown from the awake patients and 0–2 min, 2–4 min and 4–6 min after ketamine injection. BAEP can be identified easily. MLAEP show large amplitudes and a characteristic periodic waveform. During general anaesthesia, BAEP and MLAEP can be identified as in the awake state. There was no change in latency and amplitudes of MLAEP.

PATIENTS AND METHODS

Institutional Ethics Committee approval and informed consent were obtained to study 20 patients (ASA I and II, ages 20–50 yr) undergoing elective minor gynecological or urological surgery. After oral premedication with flunitrazepam 1–2 mg, 45–60 min before anaesthesia, continuous ECG recordings were commenced, a vein was cannulated and a pneumatic device was attached to the patient to obtain automatic oscillatory arterial pressure measurements every 1 min. General anaesthesia was induced with ketamine 2 mg kg\(^{-1}\) i.v. After loss of consciousness (no response to verbal commands, loss of eye lash reflex), the patient’s lungs were ventilated with 100% oxygen via a face mask. Vecuronium 0.1 mg kg\(^{-1}\) was given, the trachea was intubated and controlled ventilation with 100% oxygen commenced.

The electrodiagnostic system Pathfinder I (Nicolet Instruments) was used for auditory stimulation, registration and analysis of evoked potentials, as described in the accompanying paper [1]. Auditory evoked potentials were recorded awake and on line with the start of the ketamine injection until 6 min after the ketamine injection. One AEP averaged out of 1000 responses with a stimulation rate of 9.3 represented approximately a 2-min period: AEP 1 = awake; AEP 2 = 0–2 min; AEP 3 = 2–4 min; AEP 4 = 4–6 min after ketamine injection. For every situation, one interindividual grand average was calculated from the individual AEP.

For statistical comparison of the peak latencies V, Na, Pa, Nb, P1 and the peak amplitudes Na/Pa, Pa/Nb and Nb/P1, the Wilcoxon test was used. P < 0.05 was considered statistically significant. Statistical analysis included Bonferroni’s correction (α-adjustment).
the peaks V, Na, Pa, Nb and P1 compared with the awake state. The only difference between the AEP awake (AEP 1 and 2) and the AEP during anaesthesia (AEP 3 and 4) was a decreased high frequency muscle artefact during anaesthesia because of the use of a neuromuscular blocking drug.

The same results were obtained in the inter-individual grand average of the 20 individual AEP (fig. 2). MLAEP of the awake patients had large peak-to-peak amplitudes and a periodic waveform. During anaesthesia with ketamine there was no increase in MLAEP peak latencies or decrease in MLAEP peak amplitudes; MLAEP showed exactly the same pattern as those of awake patients, indicating that the electrophysiological condition of primary stimulus processing in the primary sensory cortex is preserved under ketamine anaesthesia.

Mean (SD) latencies of the peaks V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the patients when awake, 0–2 min, 2–4 min and 4–6 min after ketamine injection are presented in table I. In the awake state, mean latencies of peaks V (5.84 (0.31) ms), Na (18.6 (2.31) ms), Pa (30.4 (3.14) ms), Nb (47.5 (8.23) ms) and P1 (66.8 (13.2) ms) and relative amplitudes of Na/Pa (1.64 (0.73) μV), Pa/Nb (1.05 (0.67) μV) and Nb/P1 (0.76 (0.47) μV) were within the normal range. During general anaesthesia with ketamine, there was no significant increase in the latencies of V, Na, Pa, Nb, P1 and no decrease in the amplitudes Na/Pa, Pa/Nb and Nb/P1 compared with the awake state. With ketamine all features of the MLAEP corresponded to the preanaesthetic values of the awake patients.

DISCUSSION

With volatile anaesthetics, brainstem components of the auditory evoked potential are prolonged in latency only slightly. In contrast, mid-latency components show typically a dose-dependent increase in latencies and a decrease in amplitudes. At approximately 1 MAC isoflurane, MLAEP components are suppressed almost completely [4]. Initial transduction of auditory stimuli remains intact and auditory stimuli can be processed up to a brainstem or midbrain level. In contrast, processing of auditory stimuli is blocked at the level of the primary auditory cortex.
the primary sensory cortex remained unchanged, but the primary processing of sensory stimuli in contrast, our results demonstrate that, with ketamine and especially with $\text{S}(+)$ketamine (one of the two optical isomers of racemic ketamine), but $\text{R}(-)$ketamine has little effect on general EEG activity. This indicates that an induction dose of ketamine did not suppress auditory stimulus processing in the primary sensory cortex. The effect of larger doses of ketamine on MLAEP has not been investigated and further studies are required to elucidate dose-dependent effects.

In contrast to these volatile anaesthetics, ketamine apparently had a different effect on MLAEP. An induction dose of ketamine did not suppress mid-latitude components. Peak latencies and amplitudes did not change compared with MLAEP in the awake state. Several investigators have demonstrated that the generators of the MLAEP are localized in the primary auditory cortex of the temporal lobe [5—10]. This indicates that an induction dose of ketamine did not suppress auditory stimulus processing in the primary sensory cortex. The effect of larger doses of ketamine on MLAEP has not been investigated and further studies are required to elucidate dose-dependent effects.

Spontaneous EEG and processed EEG (median and spectral edge frequency) can be suppressed with ketamine and especially with $\text{S}(+)$ketamine (one of the two optical isomers of racemic ketamine), but $\text{R}(-)$ketamine has little effect on general EEG activity [11, 12]. These findings cannot be transferred to the recording of stimulus-evoked EEG signals such as auditory evoked potentials. In contrast, our results demonstrate that, with ketamine, the primary processing of sensory stimuli in the primary sensory cortex remained unchanged, although global cortical activity may be reduced, as demonstrated by EEG studies. A dose-dependent block of primary auditory stimulus processing, as shown for volatile anaesthetic agents, cannot be achieved with an induction dose of ketamine. Thus a disruption of sensory processing or a disconnection of processed information from conscious representation may occur at a higher cortical level.

One question based upon these findings is if intact stimulus processing, as demonstrated with evoked potentials, is required in order to allow higher cortical stimulus processing (stimulus evaluation) during general anaesthesia. The relation between MLAEP and conscious awareness, explicit conscious recall and response to verbal commands in surgical patients and anaesthetized volunteers during different sub-MAC concentrations of nitrous oxide and isoflurane have been investigated [13, 14]. When MLAEP peak latencies were increased significantly compared with the awake state, no conscious awareness, recall or response to verbal commands were observed. In contrast, when MLAEP were increased only slightly during anaesthesia, a high incidence of arousal was found. The AEP variables were related significantly to the level of response and fitted the response more closely than end-expiratory gas concentrations. Furthermore, it has been shown that the preserved MLAEP during general anaesthesia correlates with intraoperative motor signs of wakefulness [14—16]. In patients undergoing Caesarean section, MLAEP indicated periods of intraoperative consciousness and correlated well with the postoperative recall of surgical manipulations [17]. It has been shown also that, during phases of intact MLAEP during cardiac surgery, acoustic information presented during operation can be perceived and remembered implicitly in a postoperative interview [18]. Therefore, normal MLAEP with ketamine anaesthesia indicate that perception of auditory information may not be suppressed completely.

In investigations with ketamine and evoked potentials of other sensory modalities indicate that the cortical excitability in the primary sensory cortices remains unimpaired under ketamine anaesthesia. For example, ketamine had no effect on intracerebral recordings of visual evoked potentials in the primary visual cortex of Rhesus monkeys [19]. In contrast, visual evoked potentials recorded in the extrastriate visual cortex were suppressed significantly. These

![AEP and Ketamine](image)

**Fig. 2.** Interindividual grand averages of the 20 individual AEP. The MLAEP of the awake patients have large peak-to-peak amplitudes and a periodic waveform. During anaesthesia with ketamine there was no increase in MLAEP peak latencies or decrease in MLAEP peak amplitudes.

| Table 1. Mean (±SD) latencies of the peaks V, Na, Pa, Nb, P1 and amplitudes Na/Pa, Pa/Nb and Nb/P1 for the patients awake, 0—2 min, 2—4 min and 4—6 min after ketamine injection. During general anaesthesia with ketamine there was no statistically significant increase in latencies of $V$, Na, Pa, Nb, P1 and no decrease in amplitudes Na/Pa, Pa/Nb and Nb/P1 compared with the awake state.

<table>
<thead>
<tr>
<th></th>
<th>Awake</th>
<th>0—2 min</th>
<th>2—4 min</th>
<th>4—6 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (ms)</td>
<td>5.84 (0.31)</td>
<td>5.85 (0.24)</td>
<td>5.88 (0.25)</td>
<td>5.92 (0.26)</td>
</tr>
<tr>
<td>Na (ms)</td>
<td>18.6 (2.31)</td>
<td>18.3 (2.29)</td>
<td>17.8 (1.29)</td>
<td>19.0 (2.06)</td>
</tr>
<tr>
<td>Pa (ms)</td>
<td>30.4 (3.14)</td>
<td>32.1 (3.51)</td>
<td>31.5 (5.28)</td>
<td>32.9 (4.18)</td>
</tr>
<tr>
<td>Nb (ms)</td>
<td>47.5 (8.23)</td>
<td>49.9 (7.63)</td>
<td>48.1 (9.49)</td>
<td>48.7 (8.04)</td>
</tr>
<tr>
<td>P1 (ms)</td>
<td>66.8 (13.2)</td>
<td>65.6 (11.2)</td>
<td>61.3 (11.9)</td>
<td>61.6 (10.3)</td>
</tr>
<tr>
<td>Na/Pa (µV)</td>
<td>1.64 (0.73)</td>
<td>1.52 (0.70)</td>
<td>1.39 (0.73)</td>
<td>1.29 (0.54)</td>
</tr>
<tr>
<td>Pa/Nb (µV)</td>
<td>1.05 (0.67)</td>
<td>1.38 (0.84)</td>
<td>1.35 (0.76)</td>
<td>1.17 (0.68)</td>
</tr>
<tr>
<td>Nb/P1 (µV)</td>
<td>0.76 (0.47)</td>
<td>1.07 (0.81)</td>
<td>1.15 (1.09)</td>
<td>0.96 (0.87)</td>
</tr>
</tbody>
</table>
findings confirm also the dissociation between stimulus registration and processing in the primary sensory cortex and stimulus evaluation represented by higher cortical areas. Similarly, results obtained in the somatosensory modality demonstrate impaired stimulus evaluation by higher cortical areas. Potentials evoked by nociceptive stimuli are suppressed in the reticular formation of the midbrain and in the medial nuclei of the thalamus after injection of ketamine [20]. Besides the suppression of evoked responses in these areas, spontaneous neuronal activity is reduced also [21]. This leads to the conclusion that ketamine disturbs the processing and evaluation of the nociceptive stimuli in the reticular formation.

From a theoretical, neurophysiological point of view the present study, and data described in the literature, indicate that ketamine does not induce a general suppression of the perception and processing of sensory stimuli. Therefore, one might speculate on whether or not the anaesthetic effect of ketamine relies on a disturbed stimulus evaluation in secondary associative cortices. Sensory stimuli without any nociceptive character are transmitted up to primary sensory cortices under ketamine anaesthesia. These observations may support the concept of dissociative anaesthesia under ketamine—that is, a dissociation of perception and primary processing in the primary sensory cortices and secondary evaluation of sensory stimuli. According to this concept, ketamine allows primary sensory stimulus processing while nociception is blocked. The clinical observation of a high incidence of dreams and hallucinations during general anaesthesia with ketamine may be interpreted as inadequate suppression of sensory stimulus processing, or even consciousness.

REFERENCES