SENSORY INFORMATION PROCESSING DURING GENERAL ANAESTHESIA: EFFECT OF ISOFLURANE ON AUDITORY EVOKED NEURONAL OSCILLATIONS

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**SUMMARY**

There is evidence from neuropsychological and psychophysical measurements that sensory information is processed in discrete time segments. The segmentation process may be described as neuronal oscillation at a frequency of 30-40 Hz. Stimulus-induced neuronal oscillations of this frequency are found in the middle latency range of the auditory evoked potential (AEP). We have studied the effect of different end-tidal concentrations of isoflurane on auditory evoked 30-40 Hz neuronal oscillations. We studied 13 patients undergoing intra-abdominal urological and gynaecological procedures. AEP were recorded in the awake state and during end-expiratory steady state isoflurane concentrations of 0.3, 0.6 and 1.2 vol%. These incremental doses of isoflurane caused a stepwise decrease in frequency of oscillations. The decrease in oscillation frequency and sometimes the disappearance of oscillatory components may be interpreted as suppression of sensory information processing. The measurement of auditory evoked neuronal oscillations in the AEP appears to be a promising tool to monitor both sensory information processing capacity and depth of anaesthesia.

**KEY WORDS**


The aim of general anaesthesia is to suppress consciousness during surgery. However, it is not clear what mechanisms are responsible for conscious awareness, although several theories have been proposed [1–4]. Sensory information is processed in spatially separate areas within the brain. This concept of segregation of function is particularly well established for vision [5, 6]. Spatial segregation of function has an apparent parallel in the time domain, because it is suggested by several studies that information processing is not continuous in time and sensory input is processed in discrete successive steps.

If the temporal order threshold is determined for visual, auditory and tactile stimuli, similar values are obtained for each modality (20–30 ms [7, 8]). It is interesting to note that these three modalities show almost identical order thresholds, although fusion thresholds for stimuli are very different [9]. Further examples of discontinuous processing of sensory information come from histograms of choice reaction time and latencies of saccadic and pursuit eye movements. Such histograms are often multimodal with intermodal distances of 30–40 ms [10–13]. The multimodalities may be interpreted as an expression of preferred time zones set up by neuronal relaxation oscillations [12], within which reactions are located—that is, temporally segregated. In accordance with these psychophysical and neuropsychological findings, extra- and intracellular recordings in neurones demonstrate the existence of a 40-Hz oscillatory activity in the brain [14–16], which can be observed also in the spontaneous electroencephalogram (EEG) [17–19] and in sensory evoked potentials of different modalities [20–23].

The dominance of the 40-Hz oscillation is represented prominently in the midlatency response of auditory evoked potentials [20, 24]. We
have found suppression of the 40-Hz oscillatory component after induction of anaesthesia with etomidate [24]. These results indicate a potential link between the oscillatory components in the auditory evoked potential as an expression of information processing and the functional state of the brain. The aim of this study was to evaluate qualitative and dose-dependent effects of the volatile anaesthetic isoflurane on neuronal oscillations monitored in the midlatency range of auditory evoked potentials (AEP).

PATIENTS AND METHODS

Patients and anaesthesia

Following institutional Ethics Committee approval and informed consent, we studied 13 patients (aged 28–65 yr, ASA class II) undergoing intra-abdominal urological or gynaecological procedures. None of the patients had either oto-laryngological or neurological disorders or was receiving any medication. Patients were premedicated orally with flunitrazepam 2 mg, 45–60 min before the beginning of the study. To eliminate nociceptive stimuli during the operative procedure, continuous lumbar extradural analgesia (EA) was administered using 0.5% bupivacaine. The level and effectiveness of EA was tested by pinprick. Anaesthesia was induced with thiopentone 5 mg kg⁻¹ and pancuronium 0.1 mg kg⁻¹ was given to produce muscular relaxation. After tracheal intubation, the patient’s lungs were ventilated with 50% oxygen and isoflurane in air to maintain normocapnia. The end-expiratory concentration of isoflurane was monitored continuously with a multigas analyser (Siemens). AEP were measured after 15 min steady state concentrations of isoflurane 1.2, 0.6 and 0.3 vol% after a minimum time interval of 45 min after anaesthetic induction. Systemic arterial pressure was monitored invasively, and mean arterial pressure was maintained greater than 80 mm Hg. Core temperature was measured with an oesophageal probe and maintained greater than 34.5 °C using heated blankets and infusion of warmed solutions.

Recording of auditory evoked potentials

The electrodiagnostic system Pathfinder I (Nicolet Instr.) was used for acoustic stimulation, registration and analysis of evoked potentials. Rarefaction clicks of 0.1 ms and 70 dB above the normal hearing level were presented binaurally with a stimulation frequency of 9.3 Hz using acoustically shielded earphones (TDH 39). For recording, silver–silver chloride electrodes were positioned at Cz and A₁ with Fpz as ground (according to the international 10–20 system). The impedance of all electrodes was kept less than 0.5 kΩ. An epoch of 100 ms (bin width 0.2 ms) was bandpass filtered (1–1500 Hz) with an analog Butterworth-filter (roll-off 6 dB octave⁻¹) and averaged across 1000 stimulus presentations. The recording procedure was controlled visually on a monitor, and an automatic artefact detector rejected signals greater than 96% of full scale. To guarantee reliability of the signal and correct transmission and transduction of the acoustic stimuli, evoked potentials without a brainstem response (peak V) were rejected also. AEP were measured in the awake patient and then at steady state end-expiratory concentrations. One AEP represents the averaged activity during approximately 1 min.

Analysis of auditory evoked potentials

For each situation, we analysed the AEP of individual patients and an interindividual grand average (GA), calculated from the AEP of all 13 patients. Off-line data analysis was as follows: latencies of the peaks V, Na, and Pa and relative amplitudes from peak Na to peak Pa were measured. Latencies of all peaks were compared with the Wilcoxon test (two-tailed, minimum level of significance 5%, including Bonferroni’s correction). For frequency analysis of the potential, in addition to the classical Fast Fourier Transformation (FFT), a rank-correlation procedure (RCF) was used. In contrast to other frequency analysing methods, the rank-correlation method provides also a high frequency resolution for short epoch signals such as the AEP. The method is based on a non-parametric procedure for the detection of oscillations in time series [25, 26] and has been used successfully in another study [27] to determine main oscillation frequencies perioperatively by recorded AEP. The RCF was calculated for a time window of approximately 80 ms, always beginning with peak Na.

RESULTS

Auditory evoked potentials were recorded successfully in each patient. Figure 1 shows a rep-
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AEP

Time (ms)

FIG. 1. Auditory evoked potential (AEP) of an awake patient. BAEP = Brainstem-generated auditory evoked potential; MLAEP = midlatency auditory evoked potential. Arrows indicate peaks.

representative AEP of a premedicated, awake patient immediately before induction of anaesthesia. It consists of two distinct components: a brainstem-generated AEP (BAEP) and a midlatency AEP (MLAEP). For the BAEP, a prominent peak with a latency of 5.8–6.2 ms (corresponding to the brainstem potential V of Jewett's nomenclature) was found in each patient. This robust short-latency, brainstem-generated component served as a reference for a correct and successful transduction and transmission of the auditory stimulation. The brainstem potential was followed by the so-called No/Po complex in a latency range between 10 and 15 ms after stimulation. The No/Po potentials were contaminated occasionally with sonomotor potentials in the awake patients.

In the MLAEP, beginning 15–20 ms after stimulus application, a sequence of negative and positive peaks depicts a stimulus-dependent, oscillatory process. The peaks Na and Pa were identified easily in all cases. The following components, termed Nb, P1, N1 and P2 were detectable only in the awake state or during low concentrations of isoflurane.

AEP and corresponding power spectra (Fast Fourier Transformation) of the midlatency oscillations for a characteristic single patient in the awake state and during the three different isoflurane concentrations are shown in figure 2. Midlatency components beginning with peak Na and Pa were obviously reduced in amplitude and prolonged in latency with increasing doses of isoflurane, whereas the amplitude and configuration of brainstem potential V did not change with the level of anaesthesia. The FFT assigns a dominant frequency of 40 Hz to the midlatency oscillation of the evoked potential. Under general anaesthesia using 0.3% isoflurane, the observable increase in peak latencies resulted in a decrease in the leading

FIG. 2. Auditory evoked potentials (AEP) and corresponding power spectra from a single patient. The graph shows data from the awake state before induction of anaesthesia and during different concentrations of isoflurane. Note the slowing down and disappearance of the oscillatory component from the midlatency range and stability of the brainstem evoked potentials under anaesthesia, the latter indicating intact sensory transduction mechanisms.
oscillation frequency to 30 Hz. This oscillation frequency of the MLAEP decreased again with 0.6% isoflurane to an oscillation of 10 Hz and remained constant with 1.2% isoflurane.

Figure 3 shows the interindividual grand averages of AEP recorded from all 13 patients. The results of the grand averages confirm the suppression of amplitude and reduction of oscillation frequency seen in the single patient. Oscillation frequency again decreased in a stepwise manner. The first suppression in oscillation frequency was associated with isoflurane concentrations of 0.3%. Isoflurane concentrations of 0.6 vol% caused a further reduction of midlatency oscillations, whereas 1.2% isoflurane resulted in their complete abolition.

Mean values and SEM for the latencies of the peaks V, Na and Pa, and Na/Pa amplitudes are presented in figure 4. The latencies of the peaks V, Na and Pa had a low interindividual variability. A graded and statistically significant (P < 0.05) increase with isoflurane concentration was observed.
for both Na and Pa latencies. A significant \((P < 0.05)\) increase in the short latency brainstem potentials (peak V) was detectable only between the awake state and the 0.3% isoflurane. A further graded change in latency for this component under increasing concentrations of isoflurane was not seen. The Na/Pa amplitudes were significantly \((P < 0.05)\) reduced.

Figure 5 shows the means and SEM of the dominant oscillation frequency for all 13 patients according to the concentration of isoflurane. Mean oscillation frequency \((P < 0.05)\) decreased significantly from about 45 Hz in the awake state to 29 Hz with 0.3% isoflurane. A further increase of isoflurane concentration to 0.6% resulted in a small and insignificant shift to 28 Hz. With 1.2% isoflurane, oscillation frequency of the MLAEP decreased significantly \((P < 0.05)\), to 23 Hz.

**DISCUSSION**

In all patients, an oscillation frequency of approximately 40 Hz was observed in the awake state. This finding confirms the existence of a stimulus-dependent and interindividual constant oscillatory brain mechanism for sensory information processing. It is not clear if these oscillations are caused by a single generator or by a suprasegmental chain of generators. Studies have suggested, however, that oscillations of the MLAEP represent the activation of several generators situated at different brain levels [1].

Isoflurane is a non-specific acting general anaesthetic agent and induces a dose-dependent suppression of auditory evoked neuronal oscillations. The suppression of neuronal oscillations was reflected by prolongation of latencies and reduction of amplitudes of the MLAEP components, mainly the peaks Na and Pa. The observed influence of volatile anaesthetic agents on latencies and amplitudes of the MLAEP has been demonstrated previously [28–30]. Changes in these parameters have been proposed, therefore, as an objective criterion for depth of anaesthesia. Our results suggest that direct measurement of neuronal oscillations by frequency analysis seems preferable, for the following reasons.

Latencies and amplitudes of MLAEP components are connected only indirectly to these oscillations. Peaks Na and Pa, for instance, are prolonged in latency with each increment of isoflurane concentration. This does not necessarily represent disturbed sensory information processing. Prolongation of midlatency peaks might also be caused by slowed transmission of the acoustic stimulus from the receptor to the primary auditory cortex. Although Na and Pa latencies gradually increased from the awake state to 1.2% isoflurane, the difference in Na–Pa latency for 0.3 and 0.6% was the same, indicating a change in phase but not in frequency of the neuronal oscillation. This observation was confirmed by frequency analysis, which showed that neuronal oscillations were reduced significantly for 0.3 and 1.2% isoflurane only. The fact that oscillation frequency did not change with increasing concentrations from 0.3 to 0.6% isoflurane indicates that these doses did not suppress significantly those structures involved in the oscillatory process. As oscillation frequency of the MLAEP depends mainly on the Na/Pa complex, it could be expected that the underlying generators of these midlatency peaks are unaffected with concentrations of isoflurane less than or equal to 0.6%. It has been proposed recently [31, 32] that the Na/Pa complex is generated in the primary auditory cortex of the temporal lobe. Therefore, despite prolonged peak latencies, it can be assumed that concentrations less than or equal to 0.6% do not suppress sensory information processing of acoustic stimuli at the level of the primary auditory cortex.

Amplitudes are reduced gradually by isoflurane also, but have a greater interindividual variability compared with latency and oscillation measures.
This makes it difficult to evaluate adequate anaesthesia with this parameter. The only way to use amplitudes as an indicator of anaesthetic depth would be to compare pre- and intraoperative amplitudes individually. Nevertheless, amplitudes are very sensitive to biological and technical influences. Interindividual variability is caused by subjective hearing level, mass of the generator and distance between generator and electrode. Moreover, intrindividual changes might occur especially during operative procedures such as extracorporeal circulation in cardiac surgery. In these situations, alterations of skin resistance caused by sweating or reduced skin perfusion are quite common. A suppression of amplitudes, therefore, seems only a vague predictor of the functional state of the brain.

In addition to these practical implications, there are theoretical reasons for preferring measurement of neuronal oscillations as an indicator of the state of the brain under anaesthesia. The proposed neuropsychological model underlying sensory information processing is based on the existence of a time segmentation process. This process synchronizes sensory information from different modalities and by doing so allows the organism to identify sensory events in a time ordered structure [3, 33]. The clinical observation that patients often report no lapse of time during anaesthesia is relevant in this context [24]. It can be speculated that the suppression of the neuronal oscillations results in a disturbance of time perception or even in a subjective "loss" of time. This impression is different from the evaluation of time after natural sleep, which may be quite accurate [34]. In agreement with this observation, auditory evoked 40-Hz responses could be recorded during most phases of night sleep [35].

According to the underlying model of sensory information processing and temporal organization of perception [3, 36, 37], not only time perception but also consciousness in general should be interrupted when the oscillating activity is suppressed. One way of testing this hypothesis is to gain insight into the physiological mechanism of the proposed neuronal oscillations using pharmacological intervention. The anatomical localization of the neuronal oscillation generator has not yet been identified, but it is proposed that one or more generators localized in the midbrain and cortical structures produce the 40-Hz response in the EEG and sensory evoked potentials of different modalities [1].

General anaesthetic agents seem to be a useful tool to test the neuropsychological hypotheses of consciousness. With the presented neuropsychological model, suppression of the neuronal oscillations should allow the stimulus to enter the brainstem, but any higher cognitive function, such as perception or even retention in memory, should be blocked. The latter has yet to be tested. In this context, it would be of interest to investigate the behaviour of the neuronal oscillator under anaesthetic agents with psychomimetic effects such as ketamine or during anaesthetic regimens associated with intraoperative awareness such as high-dose fentanyl anaesthesia [38].

In the present study, AEP with 0.6% isoflurane still exhibited midlatency oscillations of about 30 Hz, despite prolonged latencies. This corresponds well with clinical observations of inadequate anaesthesia under these concentrations. Therefore, to guarantee suppression of consciousness and sufficient "depth of anaesthesia", isoflurane should be used only in concentrations exceeding 0.6%.

REFERENCES


