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Auditory evoked potentials

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This chapter will focus on the two auditory evoked potentials (AEP) most commonly used to assess the effects of general anesthetics on the brain, the auditory middle latency response (AMLR) and the 40 Hz auditory steady-state response (40 Hz-ASSR). We will review their physiological basis, the recording methodology, the effects of general anesthetics, their ability to track changes in level of consciousness and their clinical applications. Because of space constraints, this review will be limited to human studies.

Key words: brain; general anesthetics; consciousness; unintentional awareness; depth of anesthesia.

INTRODUCTION

Auditory evoked potentials (AEPs) are changes of the electrical activity of the brain (i.e. the electroencephalogram—EEG), produced by auditory stimuli. AEPs consist of positive and negative deflections (or waves) that follow the stimulus in a time-locked manner. AEP are produced by changes of electrical potential across neuronal membranes in the auditory system. The ability to record the AEP from distant sites on the scalp depends on four factors:[1] (1) the *number* of cells activated by the stimulus; (2) the degree of *synchronization* of this activation (the more synchronous the activation, the larger the response); (3) the geometry of the structure activated (depending on the arrangement of cells, the microscopic dipoles produced by the activation of each neuron may summate or cancel each other); (4) the ability of surrounding tissues (bone, muscle, CSF, glia) to conduct electricity.[1] General anesthetics primarily affect factors one and two and may indirectly influence factor three.

AEPs are much smaller than the EEG, and are thus not visible on the raw EEG. The circular waves produced by dropping a stone in quiet water provide a useful analogy. Dropping the stone in the sea will cause the same waves, but they will be hidden by the random fluctuations of the sea. The most common method to isolate the AEP from

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background EEG is averaging the EEG responses to multiple identical stimuli. The AEP will remain constant for all stimuli (because it is time-locked) while the background noise will vary and thus be reduced by averaging.

AEPs are classified as either *transient* or *steady-state*[1] (Figure 1). Transient AEPs are seen when rate of stimulus delivery is slow enough for the response to wear off before the next stimulus. Steady-state AEPs are seen when rate of stimulus delivery is fast enough to cause overlap of the individual transient responses. They consist of sinusoidal waveforms having the same frequency of that of stimulus delivery. To use again the stone in water analogy, with transient responses, one waits for the waves (AEP) to disappear before dropping a second stone (delivering the next stimulus). For steady-state responses, the stones are dropped at a rate fast enough for the waves to overlap. Transient responses are characterized by their latency (time between stimulus onset and the AEP) and by their amplitude. Steady-state responses are characterized by their phase (by reference to a one-cycle sine wave) and amplitude. The steady-state response evoked by stimuli delivered at rates near 40/second (and accordingly named 40 Hz auditory steady-state response (40 Hz ASSR)) (Figure 1) has been used extensively to assess anesthetic effect.

Transient responses are classified according to their latency as fast (6–10 millisecond), middle (10–50 millisecond), slow (50–250 millisecond), and late (>250 millisecond) responses. The auditory brainstem response (ABR) is a fast

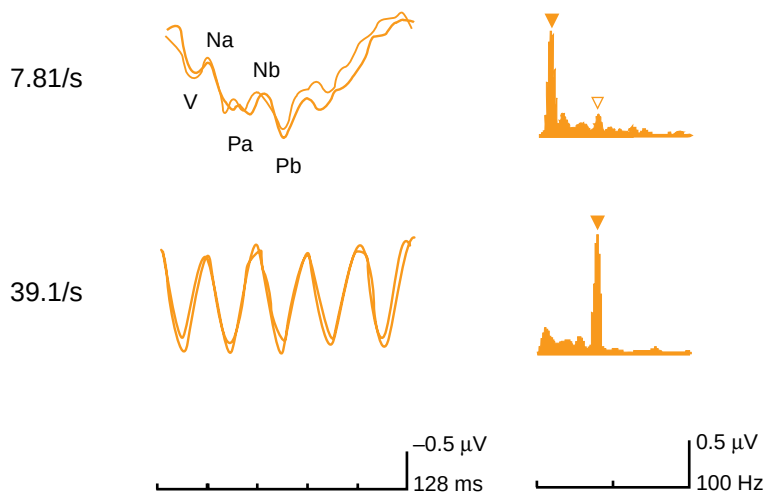

Figure 1. Transient (AMLR-top row) and steady (40 Hz ASSR-lower row) state responses. Evoked potentials were recorded in response to 500 Hz tone pips (10 millisecond duration; 65 dB above hearing threshold). The recordings were obtained between the vertex and the right mastoid with negativity at the vertex plotted upward. On the left are the evoked potentials recorded over a sweep of 128 millisecond when the tone pips were presented at rates of one or five times per sweep. Each tracing represents the average of 1000 responses. At the slow rate, several components (Na, Pa, Nb, Pb) of the AMLR are visible. At the faster rate, the 40 Hz ASSR occurs with a phase at zero-time of 142°. On the right are the amplitude spectra for the average evoked potentials. For the AMLR, most of the energy is at the rate of stimulation (closed triangle), but there is also some activity at 39 Hz (open triangle). For the ASSR, the 39 Hz region of the spectrum is markedly enhanced (closed triangle). Modified with permission from Ref. [79].

response commonly used to monitor the integrity of auditory pathways during neurosurgical procedures. It is relatively insensitive to anesthetic effects and will not be discussed further here. The auditory middle latency response (10–50 millisecond) (AMLR) (Figure 1) is, by far, the EP most commonly used to measure anesthetic effect. The slow and late responses reflect higher level of processing and are considered too sensitive to anesthetic effect for routine clinical monitoring and will not be discussed here further.

The stimuli used to produce AEP consist of clicks (brief 100 microsecond square wave) or tonebursts (brief sinusoidal waveforms). The choice of stimulus type has minimal, if any, impact for anesthesia applications. The stimuli must be delivered at intensities above hearing level, but not so loud as to be unpleasant for the awake subjects. The scalp location where the AEP amplitude is largest is usually the vertex (Cz). An earlobe or mastoid is a common reference electrode. Midline locations anterior to Cz (i.e. FPz) are also good sites and have the advantage of easier electrode application because there is no hair. A common and often overlooked problem with AEP is contamination at the response by the post-auricular muscle response (PAMR) (sound-evoked contraction of the post-auricular muscles that appears in vertex-mastoid montage as a positive wave with a latency of approximately 15 millisecond).[2] Presence of PAMR led Pockett et al[3] to conclude erroneously[4] that the 40 Hz ASSR is not a suitable monitor of anesthesia. The procedures for recording the AMLR are clearly described in Ref. [5].

AMLR

Description and cerebral generators

The AMLR consists of three main peaks: Na, Pa and Nb with nominal latency in awake subjects of 15–20, 25–30 and 40 millisecond, respectively (Figure 1). A second positive component (Pb) is sometimes present. The first letter refers to the polarity; the second, to the order of the wave. There is considerable variability in the morphology of the AMLR in normal awake subjects.[6] The AMLR can be recorded with conventional AEP recording systems or with the A-Line® (Danmeter A/S, Odense, Denmark). This device uses advanced signal processing techniques (autoregressive modeling with exogenous input[7]) to speed up signal extraction. The device also provide an index (A-Line ARX index—AAI) defined as the sum of absolute differences in the 20–80 millisecond window of the AMLR.[8] The AAI appears similar the AEP Index[9] obtained from conventional AMLR. The current version of the monitor (AEP-Monitor/2—see www.danmeter.dk) uses a composite index based on the AMLR and on the spontaneous EEG. There is limited information on this new composite index which will not be discussed further here.

The available evidence suggests that Na originates from mesencephalic structures and that Pa arises from both the auditory cortex and subcortical sources.[10] Dipole source analysis suggests that Nb arises from sources in the auditory cortex[11] or midbrain.[12] Recordings from intra-cerebral electrodes in patients with epilepsy indicate that activity occurring 30–50 millisecond after stimulus (i.e. Nb range) originate mainly from the secondary auditory cortex.[13]

Effects of general anesthetics

There is ample evidence that most general anesthetics (halothane, enflurane, isoflurane, desflurane, sevoflurane, propofol, etomidate, althesin, xenon) increase the latency and decreased the amplitude of the AMLR in a concentration-dependent manner.[14,15] Induction of anesthesia with thiopental causes a marked attenuation of the AMLR.[16]

N_2O[15] and ketamine[17] cause no change of the main components of the AMLR, even at concentrations producing unconsciousness. Opiates have no or minimal effects on the AMLR, even in large doses.[18,19] That may explain why predominantly opiod-based anesthesia is associated with a high incidence of implicit and explicit memory.[20,21] Schwender et al[22] reported that induction of anesthesia with midazolam, diazepam or flunitrazepam caused minimal, if any, alterations of the AMLR. By contrast, Brunner et al[23] reported that induction of anesthesia with midazolam causes an increase in the latency of Nb. The cause of this discrepancy is unclear. Ge et al showed that the AAI is reduced by vecuronium by $\approx$20% during steady-state anesthesia in patients without surgical stimuli.[24]

The AMLR is influenced by noxious stimulation. Thornton et al[25] reported that surgical incision increased the amplitude of wave Nb and Pb during stable anesthesia with halothane (0.3% end-tidal in 70% N_2O). Shinner et al[26] showed that tracheal intubation increases the amplitude of wave Pa and Nb during isoflurane/N_2O anesthesia. The latencies were not affected. The AAI also is increased by noxious stimulation.[27,28] These observations suggest that the AMLR reflects the balance between anesthetic suppression and brain activation caused by noxious stimulation. The response of the AMLR to noxious stimulation was no longer observed during general anesthesia with isoflurane, propofol or flumitrazepam combined with high-dose fentanyl[29] or after low dose alfentanil.[26]

Assessment of the level of consciousness

The use of neuromuscular blocking drugs carries the risk of unintentional awareness during anesthesia, i.e. the accidental regaining of consciousness during surgery by a patient who is paralyzed and thus unable to signal his or her discomfort.[30] There is therefore a need for a tool capable of reliably distinguishing consciousness (usually defined as ability to follow verbal commands) from unconsciousness. There is ample evidence that the latency of wave Nb[15,16,31–38], the high frequency (29–40 Hz) AMLR content[15,35], the AEP index/AAI[9,34,39–41] and wavelet transforms of the AMLR[37] provide reliable indication of the level of consciousness.

40 HZ ASSR

Description and cerebral generators

The 40 Hz ASSR is a sustained, sinusoidal electrical response of the brain to auditory stimuli delivered at rates near 40 Hz[42–44] (Figure 1). The label '40 Hz' is used here to denote stimulation rates between 35 and 45 Hz. Sem-Jacobsen[45] provided the first description of this response that they recorded from the auditory cortex with intracerebral electrodes. They also showed that it was attenuated by thiopental anesthesia! There is currently no commercial device using the 40 Hz ASSR for

anesthesia monitoring. Source analysis based on multi-channel scalp readings suggest that the 40 Hz ASSR arises from a midline brainstem generator with cortical sources in the left and right auditory cortex.[46] Concurrent recording of 40 Hz ASSR and functional MRI revealed similar sources.[47]

Effects of general anesthetics

The early studies with surgical patients showed that the 40 Hz ASSR was profoundly attenuated during unconsciousness produced with boluses of thiopental,[48] sufentanil,[49] propofol,[50] as well as during maintenance of anesthesia with isoflurane alone or with N_2O[48,51] or enflurane (0.5–1.1% in 60% N_2O).[52] These studies did not examine concentration-effect relationships. The impression from these studies was that: (1) the 40 Hz ASSR was almost maximally suppressed by anesthetic concentrations sufficient to cause unconsciousness (except perhaps for sufentanil); (2) that the return of consciousness was generally associated with partial recovery of the 40 Hz ASSR. Unlike other anesthetics, ketamine increased the amplitude of the 40 Hz ASSR. This effect did not appear linked to whether or not patients lost consciousness.[53]

Concentration–effect relationships were obtained for sufentanil, isoflurane and propofol. The sufentanil IC_{50} was 2.1 ng/ml.[54] A study with human volunteers[55] showed that the 40 Hz ASSR is attenuated in a concentration-dependent manner by isoflurane 0–0.5%; that the attenuation is nearly maximal at 0.5% isoflurane; that the 40 Hz ASSR is an excellent predictor of the level of consciousness. The 40 Hz ASSR is also attenuated in a concentration-dependent manner by propofol and provides a very good predictor of the level of consciousness.[56] This study also showed that using binaural stimulation increases the 40 Hz ASSR amplitude during awake baseline without changing the amplitude recorded during unconsciousness, thus increasing the contrast between awake and anesthetized values. Unconsciousness induced by individual titration of sevoflurane (mean 0.85% end-tidal concentration) reduced the ASSR amplitude by more than 70%,[57] a finding similar to the effects of propofol. Munglani et al[58] examined the effect of isoflurane (0–0.8%) on the stimulus rate producing the largest ASSR with little or no power in the harmonics, rate called the coherent frequency (CF). The CF is about 33 Hz in awake subjects and 15 Hz during unconsciousness.

The above evidence collectively suggests that the 40 Hz ASSR provides a fairly reliable measure of the level of consciousness. These observations suggest but do not prove that there is functional relationship between the attenuation of the 40 Hz ASSR and loss of consciousness. Loss of consciousness and attenuation of the 40 Hz ASSR (or of the AMLR, BIS,…) could, however, be effects that both result from the presence of the anesthetic in the brain but that are otherwise functionally independent. Consider the following example. When there is pouring rain in London, you see umbrellas popping up and car windshield wipers in motion. An outside observer, noting that these two events consistently occur together, might be tempted to conclude that they are functionally related. In an attempt to establish a stronger link 40 Hz ASSR and the level of consciousness, we have used physostigmine (a central acting cholinesterase inhibitor) to antagonize the hypnotic effects of propofol[59] and sevoflurane[57] while keeping the concentration of the anesthetic constant. Physostigmine restored consciousness in 10 of 11 volunteers who had been rendered unconscious by propofol. In the 10 subjects who regained consciousness, there was a concomitant increase of the 40 Hz ASSR to awake baseline values. The 40 Hz ASSR remained unchanged in the other subject.[59]

Physostigmine was not as effective in restoring consciousness during sevoflurane anesthesia (0.85% mean end-tidal concentration).[57] Of eight subjects, two regained consciousness, three regained wakefulness (they opened their eyes but did not follow verbal commands) and three showed no behavioral changes. There was a modest but statistically significant increase in the amplitude of the 40 Hz ASSR in the five subjects who showed a behavioral change. The 40 Hz ASSR remained unchanged in the three non-responders. The attenuation of the 40 Hz ASSR by general anesthetics thus seems to reflect the impairment of consciousness since, antagonism of the hypnotic effect of the anesthetics by physostigmine is associated with an increase in the amplitude of the 40 Hz ASSR that matches the magnitude of the hypnotic reversal.

RELATIONSHIPS BETWEEN THE AMLR & 40 HZ ASSR

There are complex relations between the AMLR, 40 Hz ASSR and spontaneous EEG rhythms.[44] The AMLR contains energy near 40 Hz (Figure 1). The interval from Na to Nb approximates a 1 cycle sinusoid with a period of $\approx$25 millisecond, which corresponds to a frequency near 40 Hz.[60] In the original description of the 40 Hz ASSR, Galambos et al[42] suggested that the 40 Hz ASSR resulted from the superimposition of the AMLR. With slow stimulus rates ($\approx$10/second) the AMLR is finished before the onset of the next stimulus. With stimulus rates near 40/second, the next stimulus occurs during wave Pa of the AMLR evoked by the preceding stimuli, thus allowing progressive build-up of the 40 Hz ASSR by superimposition of the individual AMLR. For awake, non-medicated subjects, the 40 Hz ASSR can be predicted from the AMLR[61] but the prediction is not accurate during sleep.[62] We have examined the effect of enflurane/N_2O anesthesia on the AMLR and 40 Hz ASSR and found that attenuation of the 40 Hz ASSR was much more pronounced that predicted by alterations of the AMLR.[52] This therefore suggests that the 40 Hz ASSR partly arises from synchronization of naturally occurring neuronal rhythms[63] (that are affected by general anesthetics[64]) or that general anesthetics interfere with the superimposition process (possibly by not uniformly affecting the refractory period of the AMLR components). Another indication that the 40 Hz ASSR does not solely arises from the AMLR is that the magnetic equivalent AMLR and 40 Hz ASSR are generated in different areas of the superior temporal plane.[65]

CONCLUSIONS

There are at least two reasons to search for neurophysiological measures of anesthetic action on the brain: (1) to discover the mechanisms by which general anesthetics cause unconsciousness; and (2) to obtain on-line monitoring for clinical use. The AMLR and 40 Hz ASSR both offer superb opportunities to investigate anesthetic mechanisms because these responses are well understood physiologically. An example is the hypothesis[66] that general anesthetics impair consciousness by interfering with thalamocortical 40 Hz rhythms.[67–69] It is safe to assume that the anesthetic-induced changes of AEPs reflect neural events that either contribute to unconsciousness or that are affected in a similar manner to the events contributing to unconsciousness. Thus, a detailed explanation of anesthetic-induced AEP changes might well shed light on the mechanisms of unconsciousness induced by general anesthetics.

Clinical monitoring includes two main goals: determination of the level of consciousness to prevent unintentional awareness and guidance of anesthetic delivery (to minimize drug use and speed recovery). There are other worthwhile goals such as preventing unwanted hemodynamic responses, avoiding motor responses to noxious stimulus, preventing autonomic and adrenergic responses to stress[70] but I do not think that these can be achieved by monitoring only the brain. With regard to the monitoring of consciousness, both the AMLR and 40 Hz ASSR provide a reliable indication of the presence or absence of consciousness in subjects receiving a general anesthetic agent. Applicability multi-drug regimen commonly seen in clinical practice remains to be assessed, as for BIS and other monitoring modalities.[71] With regard to titration of general anesthetics once consciousness is lost, the AMLR may be suitable because the early components (Na, Pa) persist. This may apply to the AAI as well for desflurane for which AAI-based dose titration led to a reduction in the anesthetic dose[72,73] and to a shorter postanesthesia care unit stay.[72] This does not seem to apply for sevoflurane,[74] perhaps because increasing sevoflurane above 0.5 MAC has minimal effect on the AAI.[27,75] The amplitude 40 Hz ASSR does not appear useful for titration because it is already markedly reduced at loss of consciousness. Whether other parameters of the ASSR (phase alone or combined with amplitude, use of either stimulation frequencies…) could be useful has not been examined.

I believe that both the AMLR and the 40 Hz ASSR may help reduce the incidence of awareness if they are used to confirm loss of consciousness. Failure to deliver the anesthetic (empty vaporizer, disconnected IV tubing) is an important cause of awareness that could be easily detected.[76] If, on the other hand, these devices (or any other monitor such as BIS, entropy…) are used to decrease the doses of anesthetic drugs in the hope of reducing costs and speeding recovery, the incidence of awareness with recall may well increase, as proposed by others.[77] Finally let us not forget that awareness without recall can occur,[30] even when the patients experience pain[78] and that unwise use of CNS monitors may well increase its incidence, although documentation of this problem would be very difficult.

Practice points

(1) AEP monitoring provides a reliable indication of the level of consciousness.
(2) AEP monitoring can thus be used for the detection of unintentional awareness.
(3) Great diligence must be exerted to ensure adequate stimulus delivery. Failure to deliver the stimulus (ex. disconnected or broken earphone cable) would give a false impression of deep anesthesia.
(4) AEP information must not be viewed in isolation but as part of a global context based on the integration of all available clinical data (from basic clinical signs to the output of advanced monitoring devices) and knowledge.

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Research agenda

(1) For clinical research, the challenge for the near future will be to explore the applicability of this monitoring modality to real life, multi-drug regimen commonly used in clinical practice.
(2) Another topic of clinical relevance will be to explore ways to minimize the contribution of muscle artifacts to the signal.
(3) For basic research, the most important question will perhaps be to understand why does the AEP provide such a reliable indication of the level of consciousness.

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