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CHAPTER 5

Anesthetic effects on evoked potentials

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As discussed in the previous chapter (Chapter 4, this volume) on anesthetic effects and the electroencephalogram (EEG), the major target of anesthetic action appears to be synaptic function. Since electrophysiological recordings that depend on these structures will be most susceptible to depressant agents, the changes from anesthetic agents can usually be predicted by examining the anatomy of the neural pathways involved. The net effect of anesthetic agents is due to at least three synaptic-mediated effects as well as changes in physiology caused by the agents.

First is the depression of synaptic function. This effect can be generally predicted by knowing the location of synapses within the neural pathway involved and the specific synaptic receptors and peak generators being affected by the drugs. Since synaptic effects will, like the effects on the EEG, result in prominent anesthetic effects on the cortically generated responses, it is not surprising that anesthetic effects on evoked responses parallel anesthetic effects on the EEG (which is also cortically and synaptically derived). In 1967, Winters et al. (1967) proposed a schema for anesthesia effects on cortical auditory evoked potential (AEP) that mimics a similar schema for anesthetic effects on the EEG (see Chapter 4, this volume) (Fig. 1). This schema implies that anesthetic agents have two major effects on cortical evoked potentials (EPs). First, some anesthetics decrease the amplitude until the EPs is no longer distinguishable from the background noise. Other anesthetics increase the amplitude, perhaps by increasing cortical excitability. These can then lead to seizure activity or depression.

The changes of Winters imply that the major effect is on EP amplitude; however, a consideration of generators suggests the changes may be more complex. An EP generator can refer to the anatomical structure from which the potential is believed to originate, or some theoretical model of the source of the potential (or both together) (Mauguière, 2004). From the point of view of the impact of anesthetic agents, it is important to recognize that any waveform or peak in cortical EPs represents the sum of the activity of several different simultaneously active generators. The individual component generators may be affected differently by the anesthetics leading to changes in peak morphology as well as amplitude and latency. Typically, since longer latency peaks generally have more synapses involved, these peaks are effected more by anesthetics. This has been nicely shown with sevoflurane at burst suppression where only the N_{20} wave of cortical median nerve somatosensory EPs (SEPs) is preserved (Jäntti et al., 1998). This also means that the anesthetic effects can be used to study the generator sources.

The synaptic effect also changes the ability of the synapse to recover after a depolarization since ionic currents may be prolonged (Chapter 4). As such, the anesthetic effect is stimulation-rate dependent. This leads to a trade-off in response amplitude and signal averaging time for response acquisition (i.e., a slower stimulation rate produces larger amplitude responses but increases the time to average for a set number of EP averages) (Nuwer, 1986). This effect is seen in Fig. 2 where the cortical N_{20} decreases in amplitude with a higher frequency of stimulation (and "adapts" with the frequency of 1 stimulus/s). Hence, higher concentrations of anesthetics may necessitate the use of lower stimulus frequencies (Jäntti et al., 1998). Ironically, a higher

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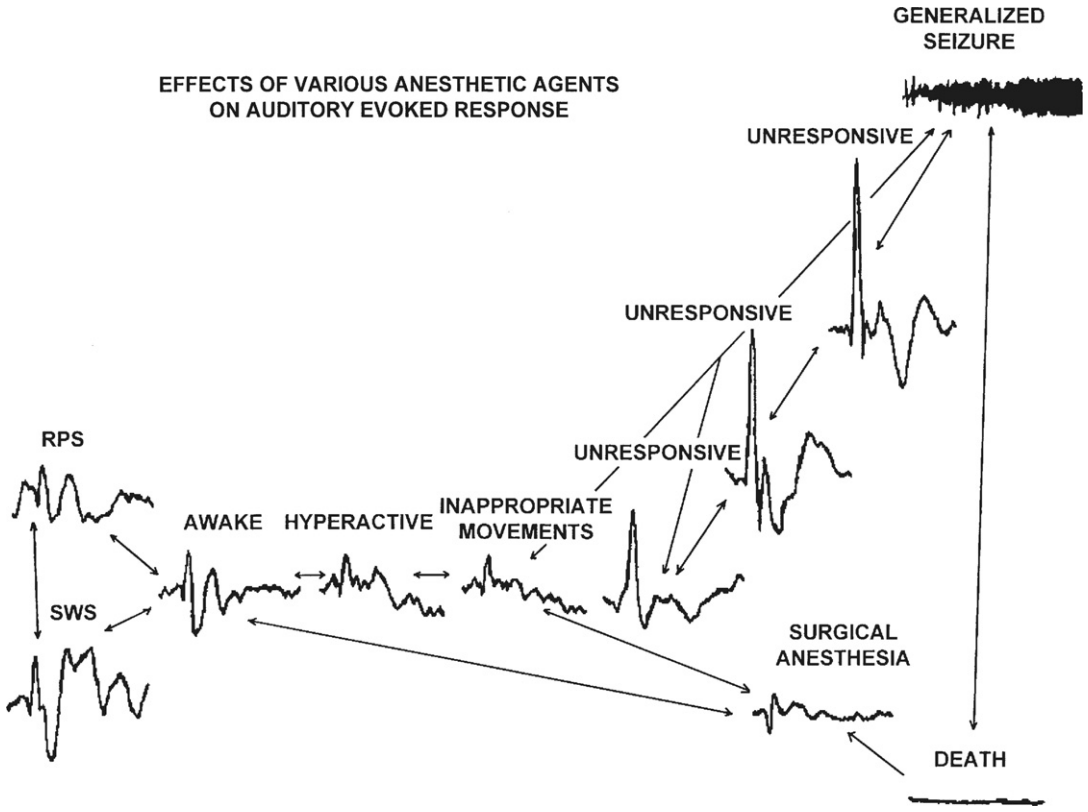

Fig. 1. Cortical somatosensory evoked potential (SEP) stages typical of anesthesia. Reproduced with permission from Winters et al. (1967) with permission from Lippincott, Williams and Wilkins.

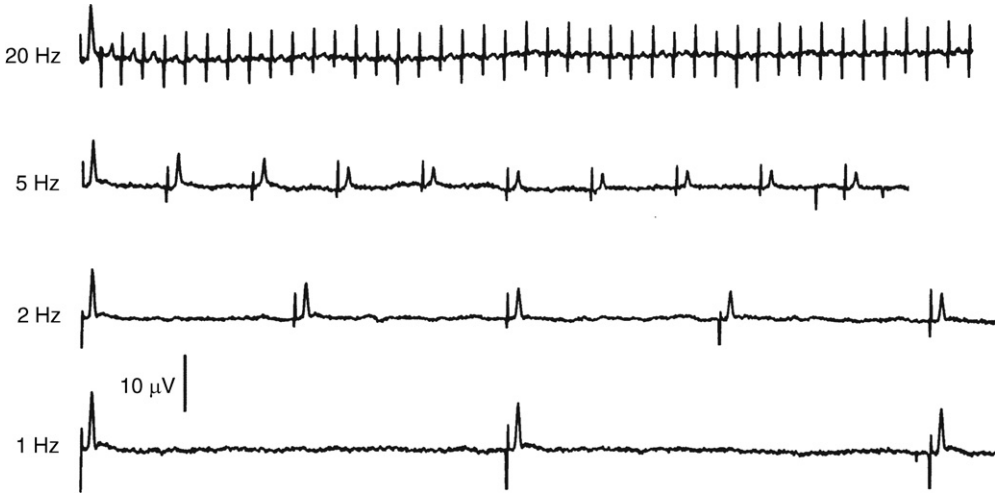

Fig. 2. N_{20} waves after median nerve stimulation in sevoflurane-induced electroencephalogram (EEG) suppression. Short spikes are stimulus artifacts, sharp wave upwards is the N_{20} wave. Note that the later cortical waves are abolished. The amplitude of the N_{20} wave decreases, that is, adapts still at the frequency of 2 Hz, and to ~1/3rd with the 5 Hz stimulation frequency, which can be used in awake subject. On the other hand, due to the high signal to noise ratio, that is, even single responses are visible, only a few responses need to be averaged for excellent quality somatosensory evoked potentials (SEPs). This recording is from P_3 to C_3 and it is a grand average from six patients. Reproduced from Jäntti et al. (1998) with permission from the International Federation of Clinical Neurophysiology.

concentration usually cause EEG suppression which improves the ratio of the EP signal to background EEG noise reducing the number of averages required (MacDonald et al., 2005). Hence, the optimal stimulation rate for each patient and anesthetic may need to be explored in monitoring. As such, this effect may also necessitate recording from different montages simultaneously because of the individual variation of potential fields of EPs.

Also of clinical relevance is that the impact on synapses and generators can change the interwave latencies because the latency of the later waves is more substantially affected. As each peak in EPs represents the sum of different generators, which are not necessarily successive (i.e., may be activated in a parallel fashion, instead of sequentially), intervals of peaks do not necessarily indicate "conduction times," and interpeak intervals may change with anesthesia in addition to physiological parameters such as neural ischemia.

The second type of anesthetic effect is the alteration in synaptic function of ancillary neural pathways that interact on the pathway that mediate the response being measured. These effects could cause additional depression, could release the current state of depression, or could result in enhancement of the responses. This effect may account for some of the effects of anesthetics which increase responses at low doses and result in depression at higher doses.

The third mechanism is the more global effect of anesthetic agents that results in the state of unconsciousness and lack of movement to painful skin incision referred to as "general anesthesia." This latter effect is not well understood, but a recent model suggests that general anesthetic agents result in changes at two major locations that will impact on evoked responses (John and Prichep, 2005). The first of these locations is action at the reflex pathways in the spinal cord. This effect is the well known effect that mediates the lack of movement with inhalational agents referred to as minimal alveolar concentration (MAC) where 50% of patients do not move to skin incision. This effect may alter spinal reflex activity and motor EPs. The second location is blockage of sensory information to the brain at the thalamus. This "thalamic gating" may explain why cortical sensory responses are substantially blocked at anesthetic doses associated with anesthesia and unconsciousness. This effect is intimately intertwined with arousal mechanisms and occurs naturally with cortical EPs as depicted in Winters's schema as changes of EPs with sleep.

As discussed in Chapter 4 on EEG, current evidence suggests that one of the major effects of several anesthetic agents involves actions on the hypothalamus that underlies slow wave sleep (SWS) by activation of the alpha receptor of the γ-aminobutyric acid ($GABA_A$) receptors (Nelson et al., 2002). The general anesthetic dexmedetomidine, a selective $alpha_2$ adrenoceptor agonist, activates the same pathways although through different receptors (Nelson et al., 2003). Slow wave sleep involves gating of sensory information at the level of thalamus, causing changes in the waveform, amplitude, and latency of cortical EPs. The highly specific GABAergic drugs etomidate and propofol as well as dexmedetomidine therefore produce a state which closely resembles SWS. This is seen both in EEG, where slow waves, vertex sharp waves, and spindles are seen. Also, the changes in EPs are similar to those during SWS (Bastuji and Garcia-Larrea, 1999; Steriade, 2000). Their latency increases, shape changes, and amplitude decreases. It is therefore likely that the changes in EPs caused by GABAergic drugs are partly due to the sleep mechanisms, particularly gating of sensory information at thalamic level.

Anesthetics with significant effects on other systems in addition to GABAergic pathways typically affect the sensory EPs as well as motor potentials more than those which act mainly on the GABAergic sleep promoting systems, that is, propofol and etomidate. Anesthetics which affect mainly *N*-methyl D-aspartic acid (NMDA) receptors do not produce the typical EEG changes including sleep-like slow activity frontally and their effects on EPs are different. Unfortunately, neither EEG or EPs give reliable estimate of consciousness with these latter drugs (N_2O, xenon, ketamine).

Although part of the arousal mechanism is affected by anesthestics; part of them are still active in deep anesthesia (i.e., at burst suppression level). Hence, a minor novel stimulus, such as electrical stimulation of peripheral nerve or even light touch of palm or foot (Jäntti et al., 1998) can produce a burst during suppression. This means that some neural system, probably in the brainstem, detects the novel stimulus and activate an arousal system, which again activates the cerebral cortex. Interestingly, a similar sensitivity to light touch is sometimes seen after ischemic brain damage (post-ischemic myoclonus). Painful stimulation causes an arousal reaction which may consist of increase or decrease of amplitude and frequency of the EEG. Both somatosensory EP (SEP) and mid-latency AEPs (MLAEP) change

towards patterns of lighter anesthesia, although the drug concentrations remain constant (Thornton, 1991; Rundshagen et al., 1995). At a burst suppression level of the EEG, sensory stimuli readily produce bursts, which is due to arousal (Derbyshire et al., 1936; Hartikainen et al., 1995). In sevoflurane and isoflurane anesthesia, the evoked responses to somatosensory stimulation are preceded by the short latency cortical component and the onset of burst is of constant waveform (i.e., a long latency EP). With propofol, the evoked complex during suppression consists of the short latency SEP, a vertex sharp wave, the slow wave burst, and a spindle, each from different generators (Huotari et al., 2004). Painful stimulation can, in fact, change burst suppression to continuous EEG in isoflurane anesthesia.

Thus, to fully explain the effects of anesthesia, EPs must be viewed in the context of effects on the synapses, generators, ancillary pathways, and complex mechanisms of sleep and unconsciousness. In addition, the nonneural effects, such as those due to alterations in cardiovascular physiology (e.g., changes in blood flow or blood pressure) may also result in neural changes. All of these, no doubt, account for the differences between individual agents, even if the specific actions are not completely understood.

5.1. Inhalational anesthetic agents

The parallel between the effects of anesthetics on the EEG and EPs has been observed in the SEP, where agents alter the cortical SEP in parallel to their effects on the EEG (Himwich, 1951). Since most drugs in common use today produce a dose-related depression of the EEG, they decrease the evoked response (decrease in amplitude and increase in latency), making the choice of anesthetic medications challenging during intraoperative monitoring of the cortical SEP.

The effects of anesthetic depression have been shown in an extensive study by Angel (Angel and Gratton, 1982), in which numerous anesthetic agents were examined using the cortical SEP from forepaw stimulation in the rat. All of the agents studied produced a dose-dependent decrease in amplitude and increase in latency. An effective dose was calculated for 50% depression of amplitude (ED_{50}), which correlated with the lipid solubility of the agents, which is known to correlate with anesthetic potency (Meyer-Overton theory). This suggested that the cortical EP changes paralleled anesthetic depth. This creates the possibility that cortical evoked responses can be used for the assessment of anesthetic effect and has been used in a device based on the cortical auditory response.

Although the effects of anesthetics on EPs appear to parallel their anesthetic potency, specific anesthetic agents may differ depending on the specific loci of neural structures that may be excited or depressed. This effect was nicely demonstrated by Rosner, who reviewed the dose-related effects of several anesthetics on different neural areas (notably the mesencephalic reticular formation, thalamus, and cerebral cortex) (Rosner and Clark, 1973). Rosner demonstrated that differences in neural depression and excitation correlated with differences in EEG patterns with increasing doses of the agents studied. Rosner ordered anesthetic agents based on the ability to depress cortical evoked responses (nitrous oxide > ether > chloroform > halothane, methoxyflurane, and trichloroethylene).

Consistent with Winters's proposal and the effect on the EEG, enflurane has the capability of causing an increase in cortical excitability (including seizures under some condition), which appears to enhance cortical EPs. This effect has been observed in the rat visual EP (VEP) and auditory brainstem response (ABR) using depth electrodes at concentrations over 1.5% (Yeoman et al., 1980; Haghighi et al., 1990a).

Thus, at clinically (or surgically) equivalent depths of anesthesia, some agents (nitrous oxide) may produce a greater degree of cortical EP depression than other agents. The differences between drugs may also be explained by differing profiles on receptor types (e.g., GABA, NMDA, etc.), differing location of action (i.e., pre or postsynaptic effects), and the spectrum of effects on individual subtypes of these receptors. The differing spectrum of actions can also explain the differing action on specific neural pathways and modalities. For example, barbiturates and nitrous oxide depress the anterolateral spinal cord pathways more than the dorsal column pathways.

5.1.1. Halogenated inhalational agents

The most prominent anesthetic effects on evoked responses during clinical anesthesia are those of the potent inhalational agents; halogenated alkanes (halothane), or ethers (enflurane, isoflurane [Forane®], sevoflurane [Ultane®], desflurane [Suprane®]). These drugs have a broad action on neural structures including the GABA receptor in the synapses, on GABA receptors extrasynaptically, they antagonize

the NMDA channel, and they act via interactions in the hydrophobic region of the cell membrane bilayer on the Na^+/K^+ ATPase channel and neuronal nicotinic acetylcholine receptor. A variety of studies have been done with these agents and an understanding of their effects serves as a good reference for comparison of the other agents.

As a sensory response, the somatosensory evoked response from peripheral nerve stimulation follows the synaptic model of anesthetic effect with depression of the EEG. In general, this synaptic model suggests that the lack of synapses between stimulation of the peripheral nerve and the cervicomedullary junction should be associated with minimal changes in the responses recorded in the peripheral nerve and spinal responses. Studies of recordings at Erb's point (brachial plexus from upper extremity stimulation) and over the cervical spine (from lower extremity stimulation) show minimal changes (0–9%), that are not dose related (Peterson et al., 1986; Sebel et al., 1987). Major changes are seen above the thalamus (where the second synapse is located) and from the cerebral cortex. Consistent with "thalamic gating" of the anesthetic model, the responses above the thalamus are disproportionately effected, as seen in several studies (Hosick et al., 1971; Manninen et al., 1985; Samra et al., 1987; Griffiths and Norman, 1993).

As predicted, higher concentrations of these agents also affect the spinal cord. Changes in the H-reflex (Mavroudakis et al., 1994) confirm the effect at the spinal level. Depth electrode studies in the spinal cord suggest that halothane and nitrous oxide may have effects in lamina I–VI and thereby account for the changes seen in epidural recordings and cervical spinal recordings from posterior tibial nerve stimulation.

Some studies of the subcortical responses show anesthetic effects appear to plateau at low concentrations consistent with a minimal effect on pathways without synapses. For example, the major latency increase often occurs at 0.5–1% inspired isoflurane with minimal effects at higher concentrations. These suggest that the effect on cortical responses has a marked effect above concentrations where the animal falls asleep. This narrowed effect range has also been observed in humans. Hence the effect in the evoked responses correlate with the clinical effects on the cortex and are consistent with a synaptic effect mediating both the effects of sedation as an anesthetic effect and mediating the cortical evoked response effect. Studies in children demonstrate that the predominant effect is above the level of the thalamus as predicted (N_{19}–P_{22} and above) (Da Costa et al., 2001) and specific studies of the spontaneous and evoked output of the thalamic relay nuclei ventroposterior and lateral (VPM, VPL) suggest that these nuclei may be an important location for the anesthetic modulation of afferent stimuli (Detsch et al., 1999). Since this level of anesthetic is 0.3–0.5 MAC, it may explain why many cortical sensory evoked responses (such as the SEP) can often be recorded with concentrations of about 0.5–1 MAC. Interestingly, the nonlinear effect is also supported by neuronal network modeling of the SEP effect based on the known effect of anesthetic agents on neurons (Ting et al., 2003).

These predictions mirror what is seen in practice (Shimoji et al., 1984). Shown in Fig. 3 are the effects of isoflurane on the responses recorded in the epidural space, on the skin over the cervical spine (Fig. 4), and over the sensory cortex (Fig. 5) after stimulation of the posterior tibial nerve. As clearly seen, these responses mirror the predictions. Further, also as shown in Fig. 5, the loss of cortical amplitude is nonlinear at isoflurane concentrations just above those where unconsciousness occurs.

This anesthetic effect is also seen with the auditory response (Dubois et al., 1982; James et al., 1982; Thornton et al., 1983, 1984; Manninen et al., 1985; Schmidt and Chraemmer-Jorgensen, 1986; Sebel et al., 1986; Heneghan et al., 1987; Sainz et al., 1987; Newton et al., 1989; Lloyd-Thomas et al., 1990; Sharpe et al., 1997a,b). The ABR

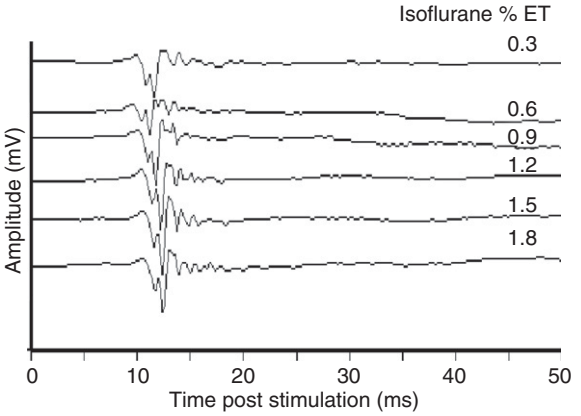

Fig. 3. Somatosensory evoked potential (SEP) responses recorded in the epidural space of a baboon following posterior tibial nerve stimulation at various concentrations of isoflurane.

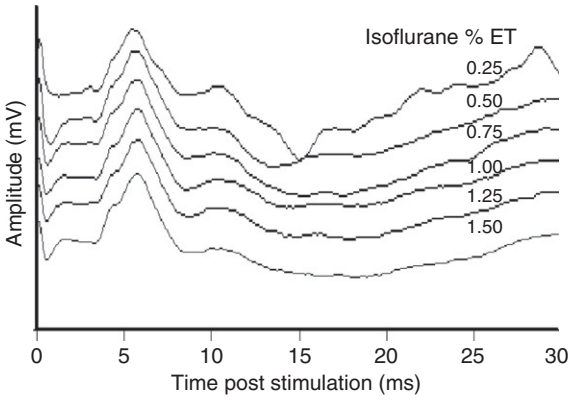

Fig. 4. Somatosensory evoked potential (SEP) responses recorded over the cervical spine of a baboon following posterior tibial nerve stimulation at various concentrations of isoflurane.

(Fig. 6) shows a progressive increase in effect as the number of synapses increases along the auditory pathway, with a substantial increase in the effect at the cortical level (Fig. 7). In fact, the effect of anesthesia on the cortically generated MLAEPs, is the basis of a device for monitoring the state of anesthetic-induced unconsciousness (Plourde, 2006). The effect on the visual evoked response is among the most dramatic, perhaps also due to the multiple synapses involved (Sebel et al., 1986) (Fig. 8).

Since the effect of the anesthetic agents on synapses will also reduce the EEG activity, the SEP responses are often recordable even when the EEG

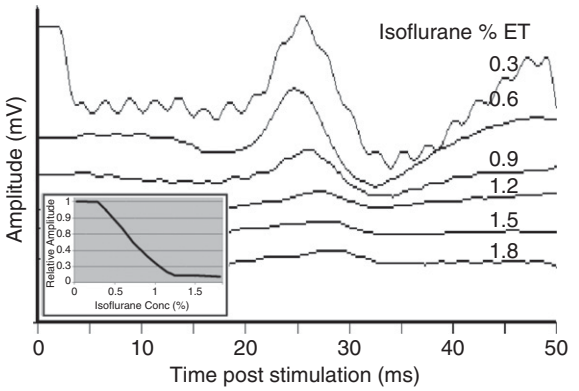

Fig. 5. Somatosensory evoked potential (SEP) responses recorded over the parietal cortex of a baboon following posterior tibial nerve stimulation at various concentrations of isoflurane. The inset on these graphs shows that the decrease in amplitude is nonlinear (occurring over a rather narrow range of concentrations).

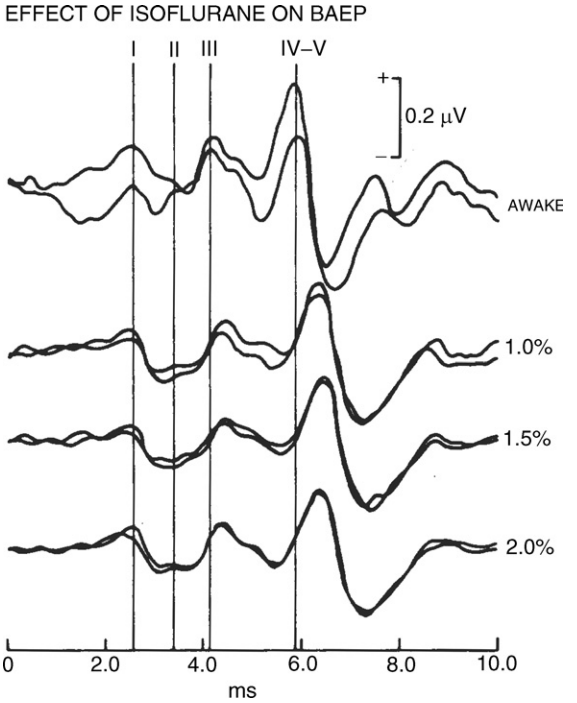

Fig. 6. Influence of isoflurane on auditory brainstem response (ABR). Latency of peaks III and IV–V are increased at 1.0% but plateau with increasing anesthetic depth. Reproduced with permission from Manninen et al. (1985) with permission from Lippincott Williams and Wilkins.

is suppressed. This effect has been observed with sevoflurane and the first cortical components are enhanced at low stimulation rates (Jäntti et al., 1998; Rytky et al., 1999). Shown in Fig. 9, the stimulus to the median nerve (spike in lower marker trace) induces an enhanced N_{20} cortical wave seen regularly after every stimulus with later waves almost totally abolished. With repeated stimuli during EEG suppression, the evoked response (N_{20}) to median nerve stimulation is seen following each stimulus, but adapts strongly when stimulation rate exceeds 1 Hz (Fig. 2). Due to the high signal-to-noise ratio, that is, lack of high-amplitude EEG and electromyographic activity (EMG), single N_{20} responses are visible (Fig. 9).

The synaptic model also helps explain the anesthetic effect in the motor pathways. Motor EPs are susceptible to anesthetic agents at three sites. The first is in the motor cortex. Stimulation of the motor cortex pyramidal cells is either by direct stimulation of these cells (leading to the production of "D waves") or indirect stimulation via internuncial

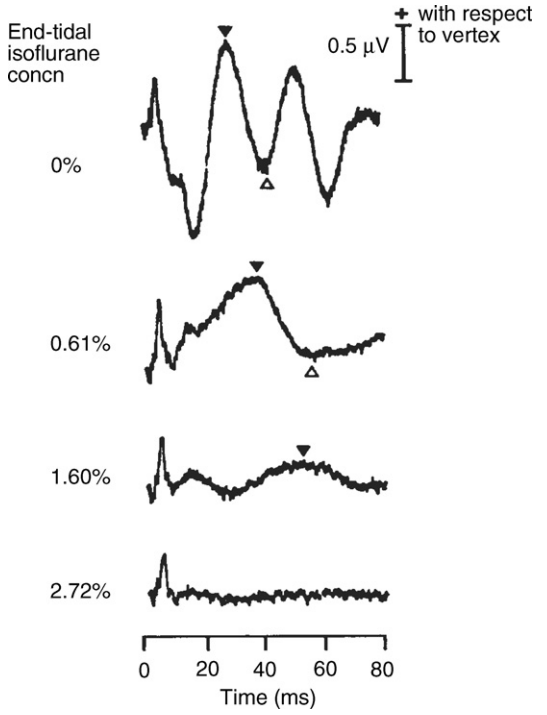

Fig. 7. Effect of increasing end-tidal isoflurane on the early cortical components of the mid-latency auditory evoked potential (AEP). The latencies of Pa and Nb increase, and the amplitudes decrease, with increasing isoflurane concentration. Reproduced with permission from Heneghan et al. (1987) © The Board of Management and Trustees of the British Journal of Anaesthesia. Reproduced by permission of Oxford University Press/British Journal of Anaesthesia.

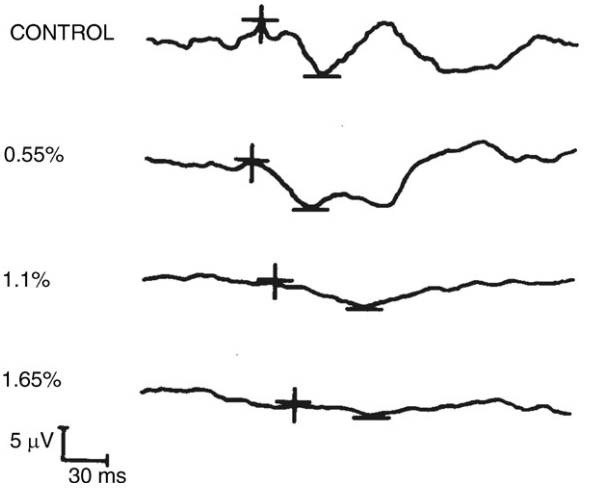

Fig. 8. Visual evoked potentials during isoflurane anesthesia. Reproduced with permission from Sebel et al. (1986) © The Board of Management and Trustees of the British Journal of Anaesthesia. Reproduced by permission of Oxford University Press/British Journal of Anaesthesia.

neurons (leading to production of "I waves"). The "D waves" are relatively unaffected by anesthetics since no synapses are involved in their production (Deletis, 1993; Yamada et al., 1994; Stephen et al., 1996; Gugino et al., 1997). I waves are generated through synaptic activity, are substantially affected by anesthetics. This is seen in the spinal epidural responses to motor cortex stimulation of Fig. 10.

Studies comparing motor EPs from transcranial magnetic (tcMMEP) and electric (tcEMEP) stimulation suggest that the magnetic technique can be more sensitive to the inhalational agents because magnetic stimulation (especially weaker field strengths) rely more on transsynaptic activation of the cortex (Sloan and Angell, 1993). High magnetic strength tcMMEP (which produces D waves) appears to overcome this difference. The synaptic dependence of tcMMEP likely also relates to the type of current pulse driving the magnetic coil since biphasic or rapidly attenuated sine wave pulses may be more effective than monophonic pulses on the production of D waves (Taniguchi et al., 1993a; Loughnan and Fennelly, 1995).

The second site of anesthetic action in the motor pathway is in the anterior horn cell. At this location, the "D" and "I" waves summate temporally. If they are able to reach threshold, the anterior horn cell depolarizes producing a peripheral nerve action potential. Partial synaptic blockade here, induced by anesthetics, may make it more difficult to reach threshold. The combined effect of anesthetics to block "I waves" from the cortex, and synapses at the spinal cord further reduce the probability of generating a compound muscle action potential (CMAP). At higher anesthetic doses, an even more profound synaptic block at the anterior horn cell may prohibit synaptic transmission regardless of the composition of the descending spinal cord volley of activity. This has suggested that the most prominent anesthetic effect on tcEMEP is at the α-motoneuron cell level (Loughnan et al., 1989; Zentner et al., 1992).

Since this is a location for the anesthetic-induced effect associated with lack of movement in response to pain (MAC), it also explains the nonlinear decrease in muscle responses associated with the induction of anesthesia. Hence, motor EPs (MEP) recorded in muscle (myogenic) are among the most easily abolished evoked responses by halogenated inhalational agents (Fig. 11). Single pulse stimulation transcranial motor evoked myogenic potentials (tcEMEP) appear to be so easily abolished by

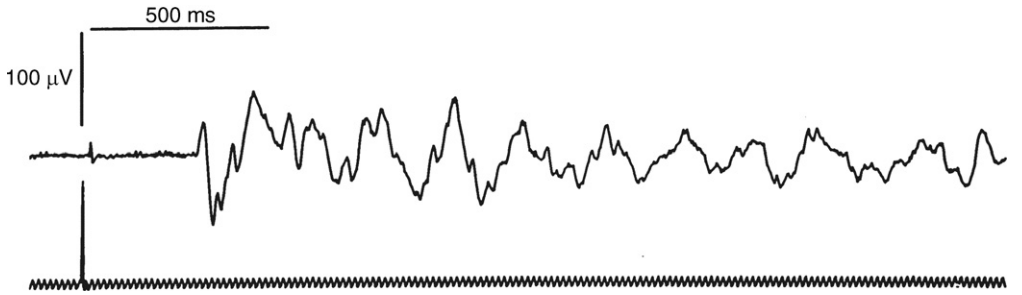

Fig. 9. Evoked responses to median nerve stimulation in sevoflurane-induced suppression. The stimulus (spike in lower marker trace) induces the enhanced N_{20} cortical wave, and the later waves are almost totally abolished. This is seen regularly after every stimulus. The burst, seen 200–300 ms later does not follow every stimulus, but it is a nonlinear (on–off) response probably induced by arousal mechanisms. Montage P_3–C_3 for upper trace. Reproduced from Jäntti et al. (1998) with permission from the International Federation of Clinical Neurophysiology.

inhalational agents that they are often unrecordable in the presence of these agents (Kalkman et al., 1991b; Stone et al., 1992). When recordable, the major effect may occur at low concentrations (e.g., less than 0.2–0.5% isoflurane) with loss of responses above 0.3–0.5 MAC (Haghighi et al., 1990a,b; Woodforth et al., 1996).

Because of the resistance of the D wave, the anesthetic effect at the α-motoneuron cell can be partially overcome at low concentrations by multiple pulse transcranial stimulation (Taylor et al., 1993; Machida et al., 1995). In this circumstance, the multiple D waves formed (and I waves if produced) summate at the α-motoneuron resulting in a peripheral nerve and motor response when cortical stimuli are placed at an interstimulus interval (ISI) of 2–5 ms (Taniguchi et al., 1993a; Taylor et al., 1993 As a consequence, low concentrations of inhalational agents appear acceptable when high-frequency transcranial stimulation is used in some patients with robust responses (Kawaguchi et al., 1996; Pechstein et al., 1998; Ubags et al., 1998). Alternatively, the anesthetic effect can also be partially overcome by activation of the H-reflex by peripheral nerve stimulation combined with transcranial stimulation (Taniguchi et al., 1991) or by stimulation of the foot sole within the receptive field of the withdrawal reflex of the tibialis anterior muscle preceding the cortical stimulus by 50–100 ms. This cutaneous input provides a spatial facilitation of the cortically elicited response yielding a larger and more reliable motor response (Andersson and Ohlin, 1999).

The third site in the motor pathway is at the neuromuscular junction. Fortunately, with the exception of neuromuscular blocking agents, anesthetic drugs have little effect at the neuromuscular junction.

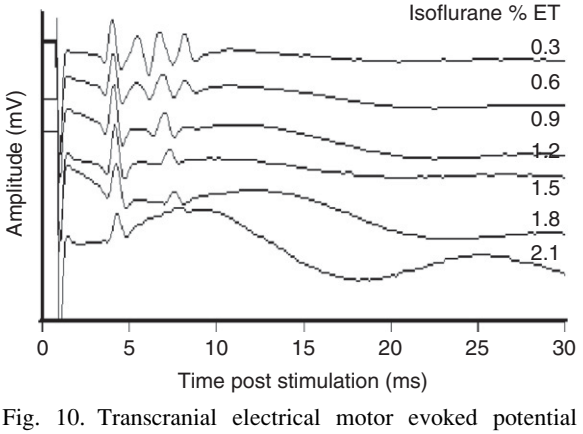

Fig. 10. Transcranial electrical motor evoked potential (tcEMEP) responses recorded in the epidural space of a baboon at various concentrations of isoflurane.

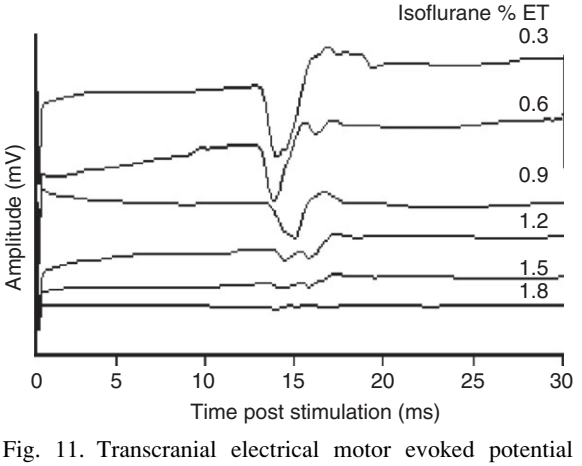

Fig. 11. Transcranial electrical motor evoked potential (tcEMEP) responses recorded in the hypotenar muscles of a baboon at various concentrations of isoflurane.

Muscle relaxants are preferred when there is recording from the epidural space or peripheral nerves but should be controlled carefully when monitoring recordings from muscles (and not used when recording spontaneous or mechanically elicited muscle responses).

Studies with evoked responses produced by spinal or epidural stimulation show minimal effects of anesthesia on recording near the peripheral nerve (neurogenic) or myogenic responses suggesting the neurophysiology of the electrical activity arriving at the α-motoneuron cell is different than from cortical stimulation (Russell et al., 1994; Schwentker et al., 1995; Bernard et al., 1996; Owen, 1997; Jou et al., 2003a). Machida studied the responses in the peripheral nerve and muscle following epidural spinal cord stimulation in the cat (Machida et al., 1995). He noticed that single pulse stimulation produced a response that was eliminated by pentobarbitol, by low-dose isoflurane and by posterior column transection (but not lateral column transection). When a pair of stimuli was used (ISI: 1–5 ms), a new complex in the peripheral nerve response was seen. This complex and the CMAP were eliminated only by high-dose isoflurane or by lateral spinal cord transection. Machida's study suggests that the type of spinal cord stimulation and the anesthetic used may alter the balance of sensory and motor contributions to the peripheral nerve and muscle response of spinal stimulation. Of interest is that the sensory tracts were more easily stimulated than motor tracts. Recent studies suggest that with isoflurane anesthesia, the motor component is preferentially blocked, perhaps by interaction at the synapses at the α-motoneuron cell or by differential effects on conduction in the spinal tracts in humans (Deletis, 1993). Based on these studies, it is conceivable that spinal stimulation techniques may monitor a mixture of sensory and motor pathways that may change with the type and dosage of the anesthetic agents used (Machida et al., 1985; Kai et al., 1993).

The inhalational agents have differing profiles. Since the anesthetic potency of inhalational agents have been traditionally assessed by MAC (the minimal alveolar concentration when 50% of subjects move in response to a painful skin incision), studies have been conducted comparing the different agents in their effect on SEP and TcEMEP at equi-MAC values. This results in a relative potency based on MAC equivalents in the order nitrous oxide (most potent) > isoflurane = sevoflurane = desflurane > enflurane > halothane (McPherson et al., 1985; Salzman et al., 1986; Pathak et al., 1989; Thornton et al., 1992; Lam et al., 1994). This difference in effect on the cortex and spinal cord may explain why the cortical effects of the agents differ at equivalent MAC levels (Rehberg et al., 1998). This difference in effect has been seen in one study where desflurane depressed the thalamocortical SEP amplitude more than sevoflurane (Vaugha et al., 2001).

The other main difference between these agents is their solubility in tissues (halothane > enflurane > isoflurane > sevoflurane > desflurane). The more the agent is insoluble, the more rapidly the concentration (and response effect) can be changed (Ku et al., 2002). Hence, desflurane may have a faster onset of effect when introduced into an anesthetic.

Conversely, some studies have compared the effects of the agents using comparable levels of the cortical effect using processed EEG bispectral index (BIS). When the BIS was adjusted to 60, the cortical amplitude of the posterior tibial nerve SEP was greater with isoflurane than with desflurane (Fletcher et al., 2005). These studies suggest that the inhalational agents do not share equivalent profiles on all of their various anesthetic effects similar to the dissimilarities in changes in cerebral physiology.

Consistent with the depression of movement by a spinal action of anesthetics, studies of spinal reflexes with inhalational agents also demonstrate depression. One study compared transcranial motor evoked responses with the H-reflex and F-wave (Kammer et al., 2002). Sevoflurane was studied at subanesthetic concentrations (0.2% and 0.4% inhaled) where the subjects were sedated but arousable at the higher concentration (thought to be two-thirds of the concentration producing sleep). The study observed significant amplitude reductions of the spinal cord responses (F response and H-reflex) to an extent much less than recordings from the cortex (i.e., alteration in the processed EEG (BIS) and amplitude reduction of the mid-latency auditory evoked response). When the amplitude of the CMAP of the transcranial MEP was reduced to 50%, the F-wave amplitude was decreased by 40%, the H-reflex by 22%, the BIS by 7%, and the mid-latency auditory evoked response was unchanged. In these studies, the M wave was unaffected confirming the minimal effect of low concentrations of inhalational agents on the neuromuscular junction and peripheral nerve conduction (Pereon et al., 1999). A similar study using isoflurane also demonstrated the depression

with the MEP being more than the F-wave (Zhou and Zhu, 2000).

This relative difference in sensitivity of the tcEMEP and F-wave and the knowledge that the inhalational agents have minimal effects on axonal conduction in nerve fibers (Bosnjak et al., 1982; Berg-Johnsen and Langmoen, 1986) suggest the inhalational agents decrease spinal motor neuron excitability, perhaps through cortical effects. Further, the prolongation of the tcEMEP but not F-wave suggests suppression of synaptic transmission in the polysynaptic motor pathways with the effect on the tcEMEP being a possible combination of these effects (Zhou and Zhu, 2000).

5.1.2. Nitrous oxide

Nitrous oxide (N_2O) is generally considered a weak anesthetic compared to the potent inhalational agents (based on MAC it is about 1/100th as potent). It is believed to have actions of antagonizing the NMDA receptor, inhibiting the neuronal nicotinic acetylcholine receptor, and exhibiting opioid-like effects on the opioid receptors. Some of its actions may be mediated through $alpha_2$ adrenoreceptors, especially in the locus coeruleus which has efferent neural connections to the thalamus and cerebral cortex (Ohara et al., 1997). Nitrous oxide is a more potent depressant of the P_{15}–N_{20} SEP response than isoflurane (Thornton et al., 1992). It has been postulated that since this response is generated in the pontine thalamic region of the brain and the locus coeruleus projects to this area, this may account for the difference between the inhalational agents and nitrous oxide (Thornton et al., 1999).

The effects of nitrous oxide vary with the other anesthetic agents being employed. When used alone, nitrous oxide tends to produce graded amplitude and latency changes in a dose-dependent manner (Fenwick et al., 1979; Benedetti et al., 1982; Chapman et al., 1982; Harkins et al., 1982; Houston et al., 1988; Zentner and Ebner, 1989), with minor or no changes in subcortical responses (Peterson et al., 1986; Schmidt and Chraemmer-Jorgensen, 1986). Because nitrous oxide is very insoluble, the changes can occur rapidly as shown in Fig. 12. When added to inhalational anesthetics, nitrous oxide may cause additional changes in latency and amplitude (Peterson et al., 1986) or have no apparent additive effect (Manninen et al., 1985; Chi and Field, 1986). Studies of equi-anesthetic mixtures of isoflurane and nitrous oxide have demonstrated that the mixture has a more potent effect on cortical SEP than would be predicted by adding the individual effects of each agent suggesting a synergism from different mechanisms of action (Sloan et al., 1995). In cases in which nitrous oxide is added to intravenous agents, amplitude changes predominate, without latency change (McPherson et al., 1985; Sloan and Koht, 1985; Zentner et al., 1989; Schubert et al., 1990). Hence, nitrous oxide may be more "context sensitive" in its effects (i.e., the actual effect may vary with the other anesthetics already present).

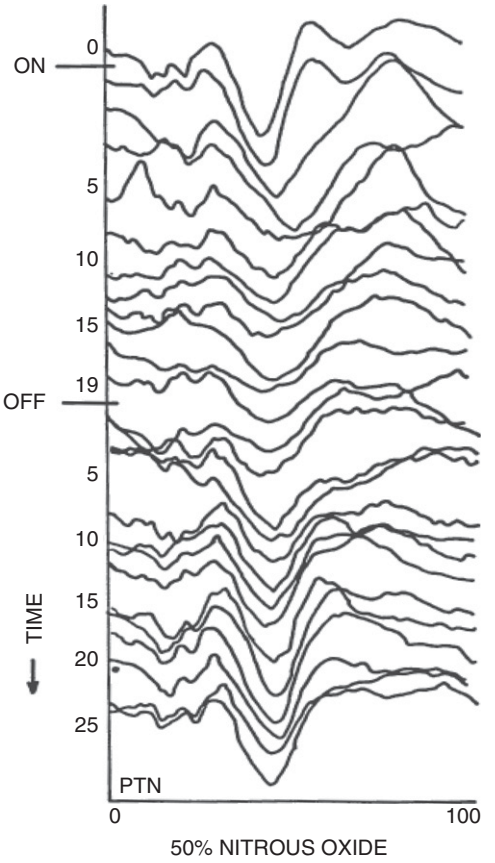

Fig. 12. Effect of nitrous oxide on cortical recordings of posterior tibial nerve somatosensory evoked potentials. The amplitude of the response is markedly reduced over the 10–15 min following the introduction of nitrous oxide and a return after agent is removed. Reproduced from Sloan and Koht (1985) with permission by Lippincott, Williams and Wilkins.

Despite its relatively weak anesthetic profile, studies with tcMMEP (Firsching et al., 1991) and tcEMEP (Jellinek et al., 1991b) show that nitrous

oxide produces depression of myogenic responses (Zentner et al., 1989; Jellinek et al., 1991b; Woodforth et al., 1996; Pechstein et al., 1998). When compared at equi-MAC anesthetic concentrations, nitrous oxide produces more profound changes in myogenic tcEMEP than any other inhalational anesthetic agent (Sloan, 1997). However, one study suggests that nitrous oxide is usually acceptable when used in concentrations below 50% (Jellinek et al., 1991b). Some studies have suggested nitrous oxide may be acceptable for monitoring with multipulse stimulation techniques; however, the other anesthetics used with it make a difference in the degree of depression (Van Dongen et al., 1999a,c; Sakamoto et al., 2001). Like the halogenated agents, the effects on the epidurally recorded MEP are minimal.

5.2. Intravenous analgesic agents

Because the inhalational anesthetic agents have marked depressant effects on cortical EPs and motor EPs, anesthesiologists frequently choose intravenous analgesics (opioids or ketamine) supplemented with intravenous sedative agents (e.g., propofol) when monitoring is required. The goal of a complete anesthetic is to use a mixture of agents to provide analgesia (pain relief), sedation, amnesia, and muscle relaxation (in some circumstances).

5.2.1. Opioid agents

Opioids (e.g., fentanyl, alfentanil [Alfenta®], sufentanil [Sufenta®], morphine, meperidine [Demerol®], remifentanil [Ultiva®]) provide excellent analgesia for anesthesia. The effect of the opioid analgesics on evoked responses is generally mild. The difference between the opioid agents and the inhalational agents likely is the result of opioid action on the opioid receptor pathways rather than the GABA and NMDA pathways. This difference in action also explains that opioids produce less sedation or unconsciousness compared to the inhalational and sedative agents (below), consistent with fewer effects at the thalamus and sensory gating.

As with minimal depression of the EEG, opioid effects on sensory and motor evoked responses are minimal on spinal or subcortical recordings. Depression of amplitude and increases of latency in cortical responses and occasional loss of late cortical peaks (over 100 ms) is seen at higher doses which produce some sedation (Ghaly et al., 1991b; Gugino et al., 1992; Kalkman et al., 1992b; Glassman et al., 1993). Fig. 13 shows that a large dose of sufentanil does produce some transient changes in the cortical SEP which largely resolves as the drug is redistributed. The effects are reversed with naloxone, suggesting that the effect is a mu receptor effect (Velasco et al., 1984; Chi et al., 1987; Lee, 1994).

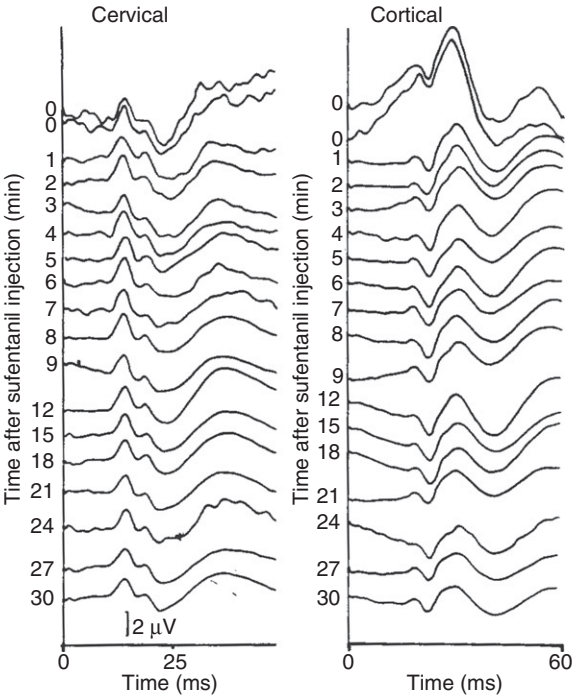

Fig. 13. Changes in median nerve cervical and cortical somatosensory evoked potential (SEP) recording with time in one patient after sufentanil 5 μg/kg. Two baseline recordings at time zero are shown. Reproduced with permission from Kimovec et al. (1990) © The Board of Management and Trustees of the British Journal of Anaesthesia. Reproduced by permission of Oxford University Press/ British Journal of Anaesthesia.

The spinal application of morphine or fentanyl produces minimal changes in the SEP, H-reflex, or spinal motor reflex (Chabal et al., 1988; Schubert et al., 1990; Fernandez-Galinski et al., 1996; Van Dongen et al., 1999a). Several studies have shown a minimal depressant effect of clinical doses of opioids on the tcEMEP (Levy et al., 1984; Zentner, 1989; Shields et al., 1990; Firsching et al., 1991; Zentner, 1991a,b; Kalkman et al., 1992b; Schmid et al., 1992; Herdmann et al., 1993; Kalkman et al., 1993; Taniguchi et al., 1993b; Stinson et al., 1994; Yang et al., 1994; Glassman et al., 1995; Jones et al., 1996; Lang

et al., 1996a; Nagle et al., 1996; Pechstein et al., 1996; Stephen et al., 1996; Ubags et al., 1996; Watt et al., 1996; De Haan et al., 1997; Gugino et al., 1997; Morota et al., 1997; Owen, 1997; Calancie et al., 1998; Pechstein et al., 1998). As a consequence of this minimal effect, total intravenous anesthesia with opioids and sedative drugs is often used when recording of responses is not possible in the presence of inhalational agents.

5.2.2. Ketamine

An alternative analgesic to opioids and the inhalational agents is ketamine. A racemic mixture of a phencyclidine derivative called ketamine acts by decreasing NMDA receptor activity, inhibiting neuronal nicotinic acetylcholine receptors, decreasing the presynaptic release of glutamate, and by opioid-like actions on the opioid receptors. It provides excellent analgesia and hypnosis, but hallucinatory activity and increases in intracranial pressure (ICP) in patients with cortical abnormalities limits its usefulness. As seen in the EEG, ketamine is an excitatory agent (probably through its interaction at the NMDA receptor) that may heighten synaptic function rather than depress it. Ketamine has been reported to increase cortical SEP amplitude (Schubert et al., 1990; Schwender et al., 1993) (Fig. 14) and increase the amplitude of muscle and spinal recorded responses following spinal stimulation at doses that do not produce spike and wave activity in the EEG (Kano and Shimoji, 1974; Glassman et al., 1993; Taniguchi et al., 1993b).

Ketamine has minimal effects been on ABR (Cohen and Britt, 1982), cortical AEP (Schwender et al., 1993; Schwender et al., 1996), VEP (Hetzler and Berger, 1984), and in myogenic tcEMEP (Ghaly et al., 1990a; Glassman et al., 1993; Kothbauer et al., 1993; Kalkman et al., 1994; Ubags et al., 1997; Inoue et al., 2002). Ketamine also increases the H-reflex suggesting that a change in alpha motor neuron excitability may contribute to the tcEMEP enhancement (Shimoji and Kano, 1973; Kano and Shimoji, 1974). High dosages, however, produce depression of the myogenic response consistent with its known property of spinal axonal conduction block (Iida et al., 1997). As such, ketamine has become a valuable adjunct during some total intravenous anesthetic (TIVA) techniques for recording muscle responses. In some studies, ketamine has been used to reduce the dose of other depressant sedatives in TIVA (e.g., propofol), or used as the sole sedative agent with resulting increase in SEP or tcEMEP (Agarwal et al., 1998; Kawaguchi et al., 2000; Erb et al., 2005).

5.2.3. Dexmeditomidine

Another agent which produces analgesia and sedation is dexmeditomidine (Precedex®). As a central, selective alpha$_2$ adrenoreceptor agonist drug, it can

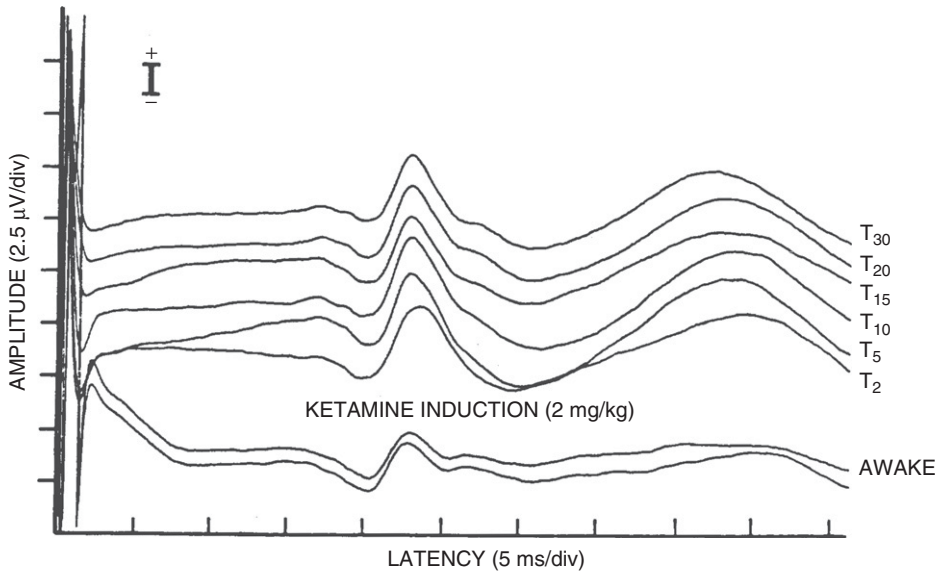

Fig. 14. Example of SEP waveforms before and after induction with ketamine at times 2, 5, 10, 15, 20, and 30 min. Reproduced with permission from Schubert et al. (1990) with permission by Lippincott, Williams and Wilkins.

provide analgesia, anxiolysis, hypnosis, and sedation. It has been used for sedation of patients in intensive care units where it provides sedation with preserved neurologic examination on arousal. Side effects of hypotension and bradycardia relate to its sympatholytic properties and limit the drug to a role as a supplement to other anesthetic agents. Dexmeditomidene was studied as a supplement to isoflurane and it caused no additional depression to the cortical mid-latency auditory response and the cortical SEP (Thornton et al., 1999). It has also been used as a supplement to propofol–fentanyl–nitrous oxide anesthetic where the later cortical peaks (P_{25}–N_{35}) of the SEP were affected but the early cortical peak (N_{15}–P_{20}) was unaffected (Bloom et al., 2001) (Fig. 15).

Clonidine, also a central alpha$_1$ and alpha$_2$ agonist (less alpha$_2$ selective than dexmeditomidine) has also been used as a supplement to opioid based anesthesia. Studies with it as an oral premedicant show no significant changes in the interpeak latencies of the ABR (Kumar et al., 1994) or on the median nerve cortical SEP (Porkkala et al., 1998). Clonidine has been given epidurally where minor changes in the dermatomal evoked lumbar and sacral responses is thought to be the result of the action of clonidine on the dorsal root afferent neurons in the spinal cord (Lund et al., 1989b).

5.3. Other analgesics

A variety of other intravenous drugs have been used to produce analgesia. Tramadol (Ultram®) is an analgesic compound that produces analgesia through opiate and adrenergic mechanisms. It is thought to exert a local anesthetic type effect on peripheral nerves. When studied in the rat by intrathecal administration, it decreased the amplitude and increased the latency of the SEP produced by sciatic nerve stimulation and recording in the epidural space (Jou et al., 2003b). It had similar effects on the CMAP recorded after stimulation of the spinal cord via electrodes in the interspinous space. Since these effects were not reversed by naloxone (Narcan®), it indicates a non-mu receptor effect, perhaps by a mechanism of sodium channel blockade similar to local anesthetics which is also seen with meperidine (Fernandez-Galinski et al., 1996; Jaffe and Rowe, 1996; Pang et al., 1998).

5.3.1. Sedative-hypnotic drugs

In some patients, excellent anesthesia for cortical evoked response recording can be provided with analgesia from opioids or ketamine, supplemented with nitrous oxide or low-dose inhalational agents. However, in some patients, the depressant characteristics of these gaseous agents reduce the size of the evoked response below that acceptable for monitoring (i.e., the desired response cannot be reliably distinguished from background noise). In these circumstances, the anesthesiologist may choose to supplement with intravenous sedative agents rather than the inhaled agents in a TIVA (e.g., opioids or ketamine for analgesia and ketamine or sedative-hypnotics for sedation).

5.3.2. Barbiturates

Barbiturates are thought to exert their synaptic effects via the GABA$_A$ receptor and they have the ability to upregulate the NMDA receptor desensitizing to stimulation. Studies demonstrate decreases

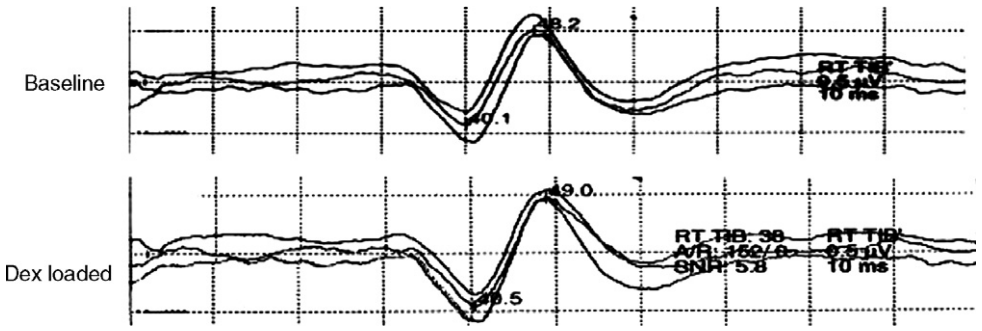

Fig. 15. Cortical somatosensory evoked responses recorded in a human during anesthesia (low-dose sevoflurane, 50% N20, and a sufentanil infusion) before and after dexmeditomidine (1 μg/kg load followed by infusion 0.3–1 μg/kg/h). Courtesy of Mary Sturaitus, MD.

in amplitude and increases in latency of cortical sensory responses with increasing effects on longer latency waves and minimal effects on the brainstem responses. Studies with thiopental (Pentothal®), a thiobarbiturate, demonstrate that the effect is minimal on subcortically recorded responses, with progressive effects on longer latency responses. For example, ABR is virtually unaffected at doses of pentobarbital that produce coma (Bobbin et al., 1979; Cohen and Britt, 1982; Newlon et al., 1983). Changes in the ABR are not seen until dosages are sufficient to produce cardiovascular collapse (Marsh et al., 1984). The SEP can similarly be recorded with thiopental sufficient to produce a flat EEG (Newlon et al., 1983; Drummond et al., 1985).

The tcMMEP, however, was more sensitive to barbiturates, with effects of amplitude depression at doses below that affecting the SEP and lasting for a longer period of time after induction. Induction with thiopental has significantly reduced (Sakamoto et al., 2001) or eliminated the tcMMEP response for as long as 45–60 min (Glassman et al., 1993). An infusion of thiopental sufficient to produce light anesthesia abolished tcMMEP (Taniguchi et al., 1993b). However, it has been successfully used in some anesthetic regimes (Zentner, 1989, 1991a,b) and given as intermittent boluses during the anesthetic (Zentner, 1991b). Methohexitol (Brevitol®) may be unusual among the barbiturates in that it is rapidly metabolized and activates seizure foci in small doses. tcMMEP has been measured when it is used in dogs, but human experience is not widely published (Young et al., 1994).

5.3.4. Benzodiazepines

The benzodiazepines, notably midazolam (Versed®), have been advocated as supplements to TIVA in routine surgery because of excellent sedation and amnestic qualities (particularly to reduce the chance of hallucinogenic activity with ketamine). They are thought to exert their effects via action at the synaptic and extrasynaptic $GABA_A$ receptors. Unlike the barbiturates, benzodiazepines have a less profound effect on the EEG suggesting a different profile on the $GABA_A$ receptor.

Midazolam, in doses consistent with induction of anesthesia and in the absence of other agents, produces a mild depression of cortical SEP (Koht et al., 1988; Sloan et al., 1990). As with thiopental midazolam produces marked acute (Schonle et al., 1989; Ghaly et al., 1990b; Kalkman et al., 1992b; Taniguchi et al., 1993b) and prolonged depression of myogenic tcMMEP (however, small doses for sedation appear tolerated; Schonle et al., 1989; Ghaly et al., 1991a; Zentner, 1991; Kalkman et al., 1992b; Scheufler and Zentner, 2002).

In addition to possible cortical locations for the benzodiazepine effect, an effect at the spinal cord has been described as antinociceptive through actions at the GABA receptors in laminae I and II in the dorsal horn (Faull and Villiger, 1986; Crawford et al., 1993). This action has been demonstrated by a study of posterior tibial stimulation where diazepam produced a marked decrease in the amplitude of the H-reflex with no effect on the M response (Kaieda et al., 1981). Since the first peak of the electrospinogram was decreased, this is consistent with a drug effect at the dorsal root. This effect has also been seen with midazolam administered epidurally in rabbits where higher doses caused significant increases in the latency of the SEP responses measured in the epidural space (Cicek et al., 2000).

5.3.5. Etomidate

As opposed to the barbiturates and benzodiazepines, etomidate (Amidate®), an imidazole derivative, can enhance synaptic activity at low doses, possibly by changing the balance of inhibitory and excitatory influences on neural pathways. It is also thought to mediate its synaptic effects via the synaptic $GABA_A$ receptors. At low doses, etomidate may produce seizures in patients with epilepsy (Rampil, 1997). This effect has been used to enhance amplitude in both sensory and motor evoked responses (Kochs et al., 1986; McPherson et al., 1986; Russ et al., 1986; Koht et al., 1988; Sloan et al., 1988; Langeron et al., 1997) (Fig. 16). Fortunately, the enhancing activity occurs at doses that are consistent with the desired degree of sedation and amnesia needed for TIVA. This amplitude increase appears coincident with the myoclonus seen with the drug, suggesting a heightened cortical excitability (however, no evidence of seizure activity was seen; Sloan et al., 1990). A sustained increase with constant drug infusion has been used to enhance cortical recordings that were otherwise not monitorable (Sloan et al., 1988).

A cat study suggests that the location of enhancement is cortical (Samra and Sorkin, 1991) which is consistent with clinical studies showing enhancement of cortical responses with no enhancement in subcortical responses (Sloan et al., 1988). In one

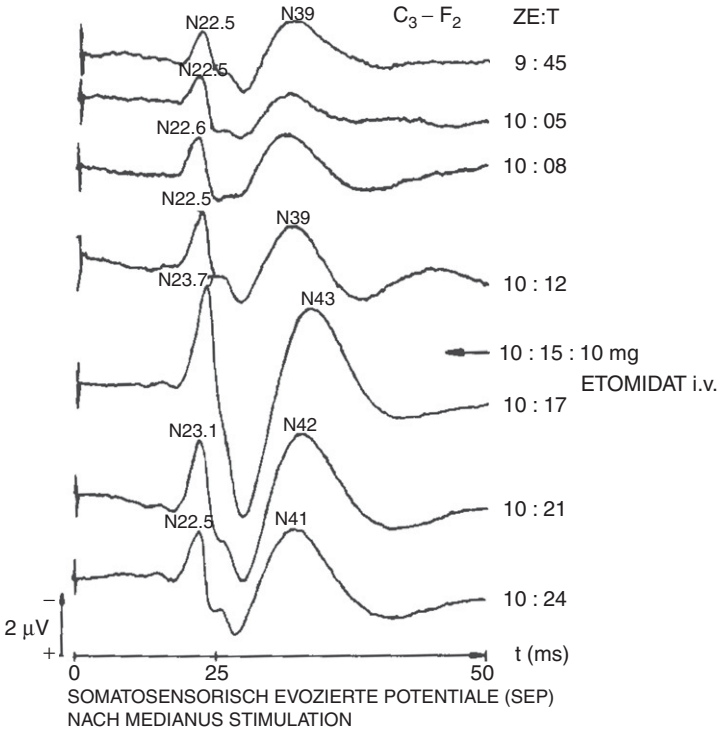

Fig. 16. Cortical somatosensory evoked potential (SEP) from median nerve stimulation before and following 10 mg etomidate. Note that the N_{20} wave and later cortical waves are enhanced. Reproduced from Russ et al. (1986) with kind permission of Springer Science and Business Media.

study, this amplitude enhancement had not resolved when the patients awakened (Liang et al., 2004). Higher doses of etomidate cause depression of the evoked responses (similar to the EEG) suggesting a biphasic effect (enhancement followed by depression). Since this would be inconsistent with a drug effect at a single synaptic site, it suggests a modulation of the degree of depression or excitation of adjacent neural pathways on the SEP pathway. This enhancement can also increase the amplitude of later cortical waves; these would normally be depressed by agents which decrease the cortical amplitude as discussed above (Fig. 16).

Studies with transcranial elicited motor EPs have suggested that etomidate is an excellent agent for induction and monitoring of this modality (Lumenta, 1991; Kalkman et al., 1992b; Glassman et al., 1993; Sloan and Levin, 1993; Taniguchi et al., 1993b; Yang et al., 1994). Of several intravenous agents studied, etomidate had the least degree of amplitude depression after induction doses or continual intravenous infusion (Glassman et al., 1993). Latency (onset) changes were not observed and amplitude enhancement of muscle responses was not observed except at very small dosages with depression at high dosages (Sloan and Levin, 1993). This effect has also been used to enhance amplitude in motor evoked responses (Kochs et al., 1986; Sloan et al., 1988).

Etomidate is also unusual in that it depresses the production of cortisol. This may not be an issue with many surgeries in which steroid agents are given routinely. However, when not given as a part of the surgery, it is unclear if supplemental steroids should be given when etomidate is used (Sloan et al., 1988).

Ketamine and etomidate are therefore unique agents in the intravenous armamentarium, as they have the ability to enhance cortical evoked responses while contributing to anesthesia. It is interesting that these two agents also increase H-reflex suggesting a change in alpha motor neuron excitability (Kano and Shimoji, 1974).

5.3.6. Propofol

Propofol (Diprovan®), an alkylphenol, is thought to act on synapses via the $GABA_A$ receptor and

extrasynaptic $GABA_A$ receptors. The drug is very rapidly metabolized such that the drug effect can usually be titrated down to levels compatible with adequate TIVA and MEP recording. It produces dose-dependent depression of the EEG reminiscent of the barbiturates and can produce burst suppression and suppression at high doses, but low amplitude activity, including spindles, can still be seen during suppression (Huotari et al., 2004).

Propofol induction produces amplitude depression in cortical AEP (Savoia et al., 1988; Chassard et al., 1989; Thornton et al., 1989; Raeder, 1996; Tooley et al., 1996), VEP (Hamaguchi et al., 2005), and cortical SEP (Maurette et al., 1988; Freye et al., 1989; Scheepstra et al., 1989) with rapid recovery after cessation of infusion (Fig. 17). Propofol does not generally appear to enhance cortical responses but one report of propofol used without other major anesthetic agents demonstrated a 15% increase in cortical SEP amplitude (Zentner et al., 1991). When the SEP is recorded in the epidural space, propofol has no significant effect. The latencies of the ABR were increased without significant amplitude decreases (Chassard et al., 1989; Purdie and Cullen, 1993). This is consistent with the postulated site of anesthetic action of propofol on the cerebral cortex (Jellinek et al., 1991a; Angel and LeBeau, 1992; Kalkman et al., 1992b; Keller et al., 1992; Taniguchi et al., 1993b; Pechstein et al., 1998).

Another advantage of propofol compared to the inhalational agents is that the dose response curve on the SEP is substantially flattened. As indicated above, the dose response curve of the inhaled agents is nonlinear with a marked effect occurring over a small range. Studies in rats indicate a more gradual change in cortical SEP amplitude with propofol blood concentrations suggesting more latitude in the titration of propofol in a TIVA infusion technique (Logginidou et al., 2003).

In addition to the practical experience with propofol which has shown its utility, studies have been done to compare propofol with the inhaled agents. When

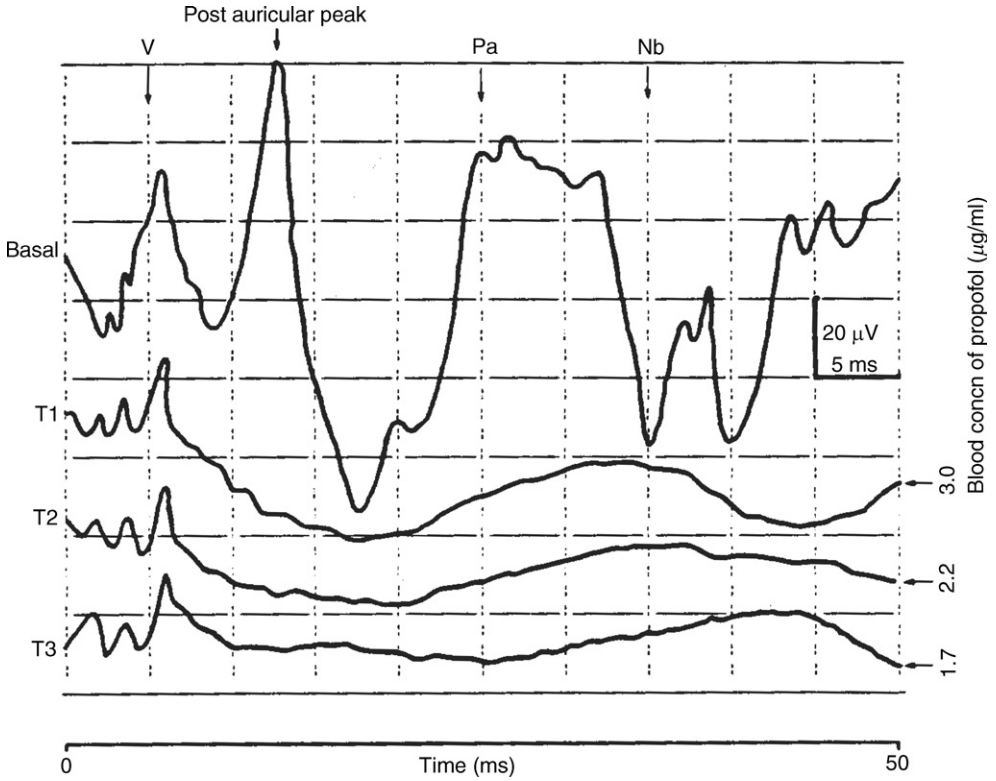

Fig. 17. Cortical (mid-latency) auditory evoked potential (AEP) before anesthesia and at different concentrations of propofol. Arrows indicate the position of waves V, Pa, and Nb. Reproduced with permission from Chassard et al. (1989) © The Board of Management and Trustees of the British Journal of Anaesthesia. Reproduced by permission of Oxford University Press/British Journal of Anaesthesia.

the BIS is used as an endpoint for anesthesia adjustment, isoflurane produced more depression of the cortical SEP amplitude from posterior tibial nerve stimulation (Chen, 2004). In this study, the effect of propofol plateaued below a BIS of 60 (where the effect was similar on latency and amplitude), whereas the effect of isoflurane continued to become more profound and the depression from isoflurane markedly diverged from propofol. Similar findings were seen with sevoflurane and propofol (delivered by a target controlled infusion) (Boisseau et al., 2002). Another study compared the effect of propofol versus isoflurane on the cortical SEP from posterior tibial nerve stimulation when the BIS was held between 40 and 50 (Liu et al., 2005). This study demonstrated a significantly lower cortical amplitude, higher cortical latency, and greater variability with isoflurane. Another study compared propofol infusion with 0.4–0.6% isoflurane with and without 70% nitrous oxide in patients undergoing scoliosis surgery with SEP and BIS. Here, the level of cortical amplitude was higher with propofol despite a lower BIS (44 vs. 61–62) suggesting a superiority for the intravenous agent (Clapcich et al., 2004). In the rat, the effect of propofol on the amplitude of the SEP was nonlinear with minimal depression of the cortical response at 20 mg/kg/h and near maximal effect at 60 mg/kg/h with essentially no effect below 20 and no additional effect above 60 (Logginidou et al., 2003).

Also consistent with a cortical effect of propofol has been the observation that only very high concentration of propofol (9 μg/ml) cause depression of the H-reflex in humans (Kerz et al., 2001). Similarly, the M wave was unaffected. Other studies have observed a dose-dependent decrease in the H-reflex amplitude and F-wave with propofol concentrations in the clinical range (Kammer et al., 2002; Kakinohana et al., 2005; Baars et al., 2006a,b). It is of interest that the suppression of the F-wave occurs at much lower concentrations of propofol (50% suppression at 1.5 mg/l) than the suppression of the BIS (50% suppression at 3.3 mg/l) confirming the suggestion that the action on the F-wave is likely by a different mechanism than the cortical effect giving rise to the BIS change (Baars et al., 2006b).

Consistent with the depression of movement by a spinal action of anesthetics, studies of spinal reflexes with low-dose propofol parallel those mentioned above with sevoflurane (Kammer et al., 2002). Hence, propofol at subanesthetic concentrations can depress the spinal reflexes with minimal cortical effect. This action is believed to be depression of spinal neuronal excitability by suppressing L-type calcium channel plateau potentials through potentiation of $GABA_A$ receptors (Guertin and Hounsgaard, 1999; Dong and Xu, 2002).

Studies with transcranial electric or magnetic elicited motor EPs have demonstrated a depressant effect on the F-wave and CMAP response amplitude, also consistent with a cortical effect (Kalkman et al., 1992b; Keller et al., 1992; Taniguchi et al., 1993b). Propofol has been used in tcEMEP when the recordings are epidural (Loughnan et al., 1989). As a component of TIVA, induction of anesthesia can include propofol (Pechstein et al., 1998) and infusions of propofol have been combined with opioids (Jones et al., 1996; Pechstein et al., 1996, 1998; Calancie et al., 1998). However, as a component of TIVA, infusions of propofol have been combined with opioids and produced acceptable conditions for myogenic tcEMEP monitoring, especially when a multipulse stimulation technique is used (Jones et al., 1996; Pechstein et al., 1996, 1998; Calancie et al., 1998). Studies comparing a propofol TIVA with isoflurane with nitrous oxide have demonstrated the superiority of the TIVA technique (Pechstein et al., 1998). In propofol monoanesthesia, tcEMEPs can usually be recorded still at burst suppression level, although their amplitude is lower than that at lighter levels (MacDonald et al., 2005).

Although acceptable recording conditions can be obtained with evoked responses, higher doses in man and animals have depressed the responses so that recording is not possible (Logginidou et al., 2003). Because of this, some TIVA methods have used ketamine to provide additional sedation so that the dose of propofol can be reduced into an acceptable range (Kawaguchi and Furuya, 2004). Ketamine also provides some analgesia in this regime and may produce some response enhancement as noted above.

5.3.7. Droperidol

Droperidol (Inapsine®) is a butyrophenone, and is a potent D_2 (dopamine receptor) antagonist with some histamine and serotonin antagonist activity. It has little effect on the EEG, but when combined with fentanyl ("neurolept anesthesia"), it increases EEG alpha activity at low doses and it produces high-amplitude beta and delta activity. Its anesthetic action is unknown but it is believed to interact at the $GABA_A$ and neuronal nicotinic acetylcholine receptor (Flood and Coates, 2002). Droperidol has been used successfully during EP monitoring. It appears to have minimal effects when

combined with an opioid on SEP (Bertens, 1988), VEP (Russ et al., 1982), and tcMMEP (Ghaly et al., 1991b; Kalkman et al., 1994). The use of a droperidol-opioid ("neurolept") technique has the additional advantage of not depressing cortical seizure activity (thus making it useful for seizure focus identification and ablation). It appears to have minimal effects on myogenic tcMMEP when combined with opioids (Herdmann et al., 1993; Taniguchi et al., 1993b). Recently, warnings have emerged regarding malignant ventricular arrhythmias and *torsade-de-pointe* with the use of droperidol (especially in patients with prolonged QT interval on the ECG) further reducing the use of this drug in anesthesia.

5.4. Local and regional anesthesia

Regional anesthesia with local anesthetics blocks conduction in the neural pathways affected causing loss of EPs. Epidural anesthesia with bupivicaine (at $L_{3–4}$) has been studied with posterior tibial SEP and dermatomal stimulation at T_{10}, L_1, and S_1 (Lund et al., 1987; Lund et al., 1989a; Dahl et al., 1990; Loughman et al., 1995). Changes were seen with 0.5% and 0.75% but not with 0.25%. The effect is similar to studies with 2% lidocaine (Loughnan et al., 1990). Loss of response has also been seen with intravenous regional block (Lang et al., 1993), specific nerve blocks (Benzon et al., 1986), thoracic paravertebral blocks (Richardson et al., 1998), as well as the topical application in areas where pain is evoked cutaneously (Svensson et al., 1993). In addition to the specific effects of local anesthetics on regional nerve function, systemically infused local anesthesia agents can cause an effect probably due to effects on sodium ion channels when given in a high dose (Javel et al., 1982; Schubert et al., 1992).

5.5. Muscle relaxants

Since muscle relaxants have their major site of action at the neuromuscular junction, they have little effect on electrophysiologic recordings that do not derive from muscle activity. Muscle relaxants are generally thought to have no effect on the sensory evoked responses (Domino and Corssen, 1964; Harker et al., 1977; Sloan, 1994). In fact, SEPs may actually improve with muscle relaxation because EMG interference is reduced in electrodes near muscle groups such as over the cervical spine. This benefit to recording is also seen in recording transcranial motor EPs

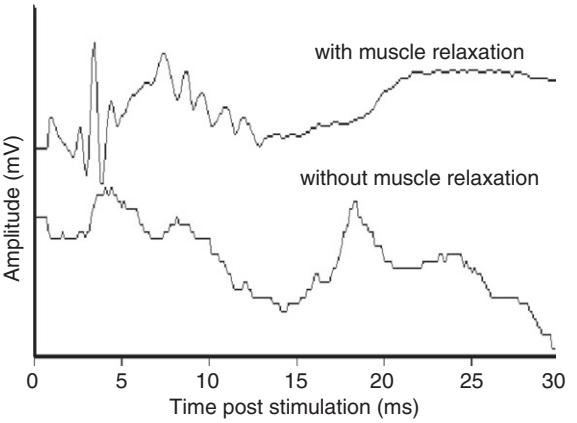

Fig. 18. Transcranial electrical motor evoked potentials (tcEMEP) responses recorded in the epidural space of a baboon at various concentrations of isoflurane with (upper) and without (below) neuromuscular blockade.

epidurally where paraspinous muscle activity can obscure recording and when recording neurogenic responses from spinal stimulation (Schwentker et al., 1995). This is true for epidural or peripheral nerve recordings where the activity of overlying muscle obscures the response from transcranial or spinal stimulation. For recording of epidural or neurogenic responses, complete or near-complete neuromuscular blockade is highly desirable (Levy et al., 1984; Rodi et al., 1996; Stephen et al., 1996). Fig. 18 shows recording from the epidural space from tcEMEP with (top) and without (bottom) muscle relaxation. Note the muscle artifact obscures the identification of I waves. This effect may be responsible for the enhancement seen with low doses of propofol (Zentner et al., 1991) and meperidine (Anonymous, 1980).

Certainly, complete neuromuscular blockade will prevent recording of muscle responses (CMAP) during MEP. However, partial neuromuscular blockade has the benefit of reducing a substantial portion of the movement which accompanies the testing and may facilitate some surgical procedures where muscle relaxation is needed for retraction of tissues. In these cases, careful monitoring of the blockade of the neuromuscular junction is critical in the muscles being monitored (since not all muscles will respond identically to the same dose of muscle relaxants).

When neuromuscular monitoring is quantitated using the amplitude of the CMAP (T_1) produced by supramaximal stimulation of a peripheral motor nerve (M response), successful monitoring of tcEMEP myogenic responses have been accomplished at 5–15% (Oro and Haghighi, 1992; Van Dongen et al.,

1999b), 10% (Nagle et al., 1996; Scheufler and Zentner, 2002), 15% (Hargreaves and Watt, 2005), 10–25% (Shields et al., 1990; Stinson et al., 1994), 20% (Herdmann et al., 1993; Glassman et al., 1995; Lang et al., 1996a,b; De Haan et al., 1997), 25% (Ubags et al., 1996), 30–50% (Yang et al., 1994; Lee et al., 1995; Gugino et al., 1997; Van Dongen et al., 1999b), and 80–90% (Kalkman et al., 1992b; Herdmann et al., 1993; Tabaraud et al., 1993; Stinson et al., 1994; Lee et al., 1995) of T_1 compared to baseline. When neuromuscular blockade is assessed by comparing the ratio of the fourth to the first twitch when stimulated at a rate of 2 Hz (called a train of four response), acceptable CMAP monitoring has been conducted with only two of four responses remaining (Pechstein et al., 1996; Calancie et al., 1998).

Although recording of myogenic responses is possible with partial neuromuscular blockade, the amplitude of the CMAP will be reduced by the blockade. Studies suggest the actual reduction varies from a linear reduction paralleling the $\%T_1$ to a slightly decreased rate of reduction (Sloan and Erian, 1993a,b) (Fig. 19). As a consequence of the amplitude reduction, the ability to record with partial neuromuscular blockade will be dependant on the neurological pathology in the pathway monitored that may reduce the baseline CMAP response. This reduction can impact on pedicle screw testing; one study of pedicle screw stimulation suggests that neuromuscular blockade exceeding 80% reduction of the single twitch may falsely elevate stimulation thresholds (Minahan et al., 2000).

It is important to note that the use of neuromuscular blockade is controversial during monitoring of muscle responses from mechanical stimulation of nerves and partial paralysis may reduce the ability to record these responses (e.g., facial nerve monitoring or monitoring for pedicle screw placement). One study of vocalis muscle monitoring (Streinzer et al., 1986) suggested that the effect of vecuronium was nonlinear with the response of the vocalis muscle being reduced to 50% of the baseline when the twitch height of the evoked adductor pollicis response was 20% of baseline under various degrees of neuromuscular blockade using accelerometry.

5.6. Physiological considerations

In addition to the specific action of anesthetic agents, the intraoperative management of patients may have physiological changes induced by anesthetic agents or surgery. Some of these changes are associated with changes in evoked responses. For example, numerous studies (Branston et al., 1974, 1976; Astrup et al., 1977; Brierley and Symon, 1979; Symon et al., 1984; Symon and Murota, 1989) have demonstrated a threshold relationship between regional cerebral blood flow (CBF) and cortical evoked responses. Although clinical function becomes abnormal at about 25 cm^3/min/100 g (the normal is 50 cm^3/min/100 g), electrical function generally remains normal when the CBF exceeds the "functional threshold" of about 22 cm^3/min/100 g (Fig. 20).

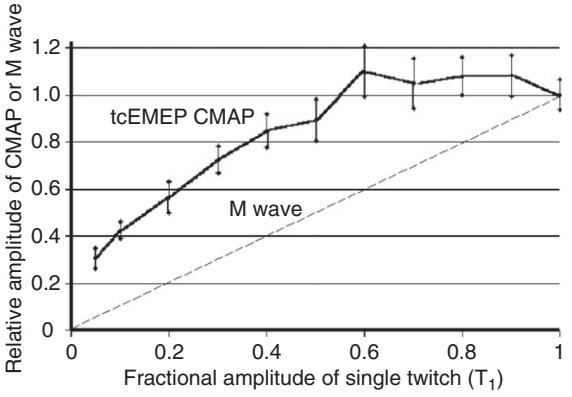

Fig. 19. Comparison of the M wave from peripheral nerve stimulation at various degrees of neuromuscular blockade (dashed line) to the amplitude of the compound muscle action potential (CMAP) from transcranial electrical stimulation.

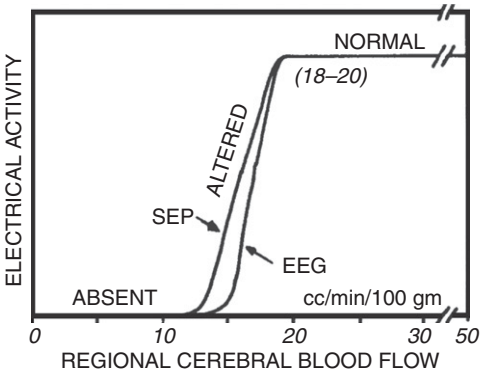

Fig. 20. Relationship between the somatosensory evoked potential (SEP) and electroencephalogram (EEG) electrical response and regional cerebral blood flow. Reproduced from Sloan (1985) with permission from Oxford University Press.

Below this level, the EEG and SEP become abnormal (Sloan 1985; Florence et al., 2004). SEP amplitude is reduced by desynchronization of the responses or a loss of functional neurons. Below this level, the impact on electrical function becomes more profound with decreases in SEP amplitude between 16 and 20 cm^3/min/100 g. At lower levels, electrical activity is lost (EEG at 7–15 cm^3/min/100 g and SEP lost between 12 and 15 cm^3/min/100 g). In some studies, the SEP is lost at CBF about 20% below the level which produces an isoelectric EEG (Prior, 1985; Nuwer, 1988).

In some experimental studies, hypotension to less than 40 mm Hg or ischemia to 20–25% of normal blood flow has not been associated with SEP changes (Laschinger et al., 1988). However, in humans during surgery, SEP changes have been observed at blood pressures which would not ordinarily be associated with neural ischemia (e.g., systolic blood pressures above 90 mm Hg systolic) (May et al., 1996). This has been thought to be the result of operative mechanical stress combined with the blood pressure reduction leading to a more profound effect than predicted by blood pressure alone (Seyal and Mull, 2002). In several of these patients, an increase in blood pressure restored the response (Brodkey et al., 1972; Griffiths et al., 1979; Dolan et al., 1980; Wiedemayer et al., 2002).

In addition to systemic hypotension, regional hypoperfusion can be detected by the evoked response if it involves the neural pathway generating the response. Examples include peripheral nerve ischemia from positioning, tourniquets or vascular interruption (Yamada et al., 1981; Grundy et al., 1982a,b; Mahla et al., 1984; McPherson et al., 1984; Fava et al., 1988; Witzmann and Reisecker, 1989; North et al., 1991), spinal cord ischemia from aortic interruption or mechanical distortion, carotid artery interruption (Russ and Fraedrich, 1984), vertebrobasilar insufficiency aggravated by head extension, cerebral artery constriction by vasospasm, and cerebral ischemia due to retractor pressure (Symon and Murota, 1989).

Studies of ischemia and anoxia in peripheral nerves show an action potential amplitude decrease to 50–60% of baseline during the first 20 min that is thought to represent temporal dispersion with slowing of the fast and slow conducting fibers rather than conduction block (Laschinger et al., 1988). These amplitude changes vary with the degree of ischemia. Since the dorsal column pathways are a continuation of the peripheral nerves, these effects may explain the decline of SEP amplitude with spinal cord ischemia. With anoxia, a latency increase in peripheral nerves occurs within 15–20 min. However, after 1 h of anoxia, the conduction velocity in the spinal cord increases suggesting a preferential loss of slow conducting pathways.

Both the white and gray matter of the spinal cord is vulnerable to ischemia and anoxia. In studies of animals which developed paraplegia following spinal cord ischemia, the animals either had both gray and white matter lesions or just white matter lesions with prolonged SEP conduction time (Follis et al., 1993). Once injured, there is usually more recovery in the white matter than the gray matter. Compound action potentials in myelinated axons (such as the dorsal columns) are attenuated rapidly with anoxia and disappear within minutes (Waxman et al., 1991). Demyelinated axons appear to have more resistance to ischemia and appear to recover faster. Demyelinated peripheral nerves also appear more resistant to ischemia (Imaizumi et al., 1998). This suggests that the SEP may be a sensitive pathway to detect spinal cord ischemia; however, if it includes pathology with demyelination it may be less sensitive than other pathways.

Another physiological variable affecting the evoked responses is raised ICP. Several studies have shown that reductions in amplitude and increases in latency of cortically generated visual, somatosensory, and auditory evoked responses occur with increasing ICP. ABR responses are altered as uncal herniation occurs (Nagao et al., 1978). SEP has been used to guide cerebrospinal fluid (CSF) pressure management during thoracic aorta procedures to reduce the risk to the spinal cord (Oka and Miyamoto, 1987; Grubbs et al., 1988; Maeda et al., 1989). The relationship of the VEP to ICP has suggested the VEP as a means of noninvasive ICP testing (York et al., 1981).

Hypoxia (similar to cerebral ischemia) is associated with SEP latency increase and amplitude decrease until the responses are lost (Colin et al., 1978; Branston et al., 1984; Koscielniak-Nielsen et al., 1998). Cortical SEP appear more sensitive to hypoxemia than the EEG and are more sensitive than the subcortical and spinal responses (Kayama, 1974; Kobrine et al., 1980; Iwayama et al., 1986). The ABR is unaffected with PaO_2 levels as low as 60 mm Hg or O_2 saturation levels of 45% (Mosko et al., 1981; Samra et al., 1984); however, acute hypoxemia to a PaO_2 of 20–30 mm Hg increased

ABR latency and decreased amplitude before loss of the response (Sohmer et al., 1982, 1989; Pierelli et al., 1986). These changes occurred despite unchanged SEP suggesting cochlear dysfunction (Sohmer et al., 1982, 1986). The VEP shows a biphasic response to a PaO_2 of 20 mm Hg with a transient amplitude increase that precedes a decrease (Kayama, 1974).

Since changes in hematocrit can alter both oxygen carrying capacity and blood viscosity, the maximum oxygen delivery is often thought to occur in a mid-range hematocrit (30–32%). Evoked response changes with hematocrit are consistent with this optimum range (Nagao et al., 1978; Merton et al., 1982; Dong et al., 1986). The combination of hemodilution and hypotension has been associated with changes that are not seen with each effect alone (Starr and Achor, 1979).

Alterations in latency and amplitude of cortically generated EPs have been observed as ventilation is altered beyond the extremes of arterial or end-tidal carbon dioxide concentrations routinely employed during anesthesia and surgery (Symon and Murota, 1989). The most significant changes occur with the carbon dioxide is extremely low ($PaCO_2 < 20$ mm Hg) and may indicate cerebral ischemia. Hypercapnea (>100 mm Hg) is associated with an increased latency (15–30%) and decreased amplitude (60–80%) of the feline cortical SEP (Browning et al., 1992). Levels of 50 mm Hg have not been associated with changes in human SEP (Kalkman et al., 1991a).

Hypothermia, either inadvertent (from a cold operating room) or intentional (such as used to provide neural protection such as with thoracic aortic aneurysm repair) is common in operating rooms where monitoring is occurring. Hypothermia can alter evoked responses by changing nerve depolarization (increased action potential duration (Klee et al., 1974), reduced conduction velocity (Kraft, 1972; Desmedt, 1989), and decreased synaptic function (Weight and Erulkar, 1976), resulting in increases in latency and decreases in amplitude of evoked responses (Dolman et al., 1986). Neurotransmitter release is enhanced at synapses leading to higher end plate potentials (Lundberg, 1948). Nerve conduction velocity is decreased increasing latency while the amplitude and duration of the nerve action potential is increased leading to variable amplitude changes (Takaki et al., 1992; MacKenzie et al., 1995). At temperatures less than 32 °C (moderate hypothermia), synaptic transmission is reduced due to impaired neurotransmitter release (Fay, 1959; Hubbard et al., 1971; Benita and Conde, 1972). Nerve conduction velocity is also impaired (to an extent less than synaptic transmission; Hubbard et al., 1971; Andersen et al., 1972; Sohmer et al., 1989) due to decreases in resting membrane potential and increases in sodium–potassium channel activation time (Klee et al., 1974). In general, peripheral nerve conduction decreases by about 5% and central conduction by 8–12%/°C (Aren et al., 1985; Russ et al., 1987; Zeitlhofer et al., 1990; Reynolds et al., 1991). The net effect on response latency is the combined effect of the conduction change and synaptic delays. Hence, late cortical waves are markedly diminished due to the cumulative effect on multiple synapses and later waves are lost before early peaks (Florence et al., 2004). The primary cortical sensory responses can be consistently recorded to temperatures as low as 19 °C in cardiopulmonary bypass (Aren et al., 1985) with the median nerve N20 being lost at about 15–26 °C and the P14 being lost at 12–20 °C (for comparison, the EEG becomes isoelectric at 22–25 °C) (Kochs, 1995; Guérit, 1999). Hypothermia appears to affect synaptic function more than conduction (Budnick et al., 1981), probably primarily by interference in the postsynaptic membrane (Weight and Erulkar, 1976). Thus, changes are more prominent at the cephalic end of long neural tracts (such as the SEP) or in components of responses associated with multiple synaptic elements. Hence, responses recorded from peripheral nerves are minimally affected, while those produced by cortical structures are markedly affected (Dolman et al., 1986; Hume and Durkin, 1986; Kottenberg-Assenmacher et al., 2003). Later waves of the ABR are similarly affected more than early waves (Stockard et al., 1978; Hett et al., 1995).

Whole body hypothermia, either inadvertent or intentional, is the most obvious temperature change that occurs during surgery. In addition, changes in regional temperature can occur and result in evoked response alterations making the site of temperature monitoring key to understanding the changes in responses (i.e., the location may not identify the temperature change or may overrepresent the extent of the temperature change). Hence, hypothermia of a limb may delay peripheral nerve responses of the SEP, but not be associated with central conduction time changes if the core temperature is maintained (Aren et al., 1985; Reynolds et al., 1991). For example, cold irrigation solutions applied to the spinal cord (Coles et al., 1983), brainstem, or cortex routinely cause evoked response changes.

Changes in a variety of other physiological variables may produce alterations in the evoked responses during surgical monitoring. Significant reduction in blood volume can alter evoked responses due to changes in blood flow distribution, despite absence of significant blood pressure changes (e.g., extremity ischemia altering the SEP as blood flow to central organs is spared). An increase in superior vena caval pressure during cardiopulmonary bypass has been associated with SEP changes (Hill et al., 1987).

Other physiologic events may occur too slowly to be noted as changes in the evoked response. For example, changes in glucose (Deutsch et al., 1983), sodium, potassium, and other electrolytes important in the neurochemical environment and affecting neural depolarization and conduction are likely to result in evoked response changes. For example, with injury (such as blunt trauma to the spinal cord), extracellular potassium increases (from 4 up to 80 mM/l) leading to axonal failure (above 10 mm/l) (Young and Sakatani, 1990). Hence, the SEP could be lost from potassium released from adjacent structures and does not require axonal disruption of the pathway. Gradual clearing of the potassium will allow restoration of the SEP with the time to recovery dependent on the initial rise in the potassium and the local blood flow. Another effect is that of bilirubin neurotoxicity which can markedly alter the ABR but cannot affect the SEP (Shapiro, 2002). This has been observed by other authors (MacDonald et al., 2003; Skinner et al., 2003) and similar changes have been seen with the SEP (Maurette et al., 1988; Lubicky et al., 1989; Kalkman et al., 1991c; Rappaport et al., 1994). Finally, changes in cortical evoked responses have been observed with pneumocephalus (Paisansathan et al., 2003).

5.7. Conclusion

In general, the effect of anesthetic agents on the evoked responses parallels the effects on the EEG (Table 1). In most patients, an anesthetic suitable for monitoring sensory and motor potentials can be found if the anesthesiologist is familiar with the monitoring methods, the underlying physiology, and the different effects of anesthetic agents. When appropriate responses are not recorded, technical changes in

Table 1

Summary of neurophysiological effects of hypnotics

		EEG	SEP	AEP	MEP
Specific GABA agonist	Propofol	Spindles, vertex-wave, B-S	↓	↓↓	↓
	Etomidate	Spindles, vertex-wave, B-S	↑	↓↓	↓
GABA and others	Halothane	B-S variable	↓↓	↓↓	↓↓
	Isoflurane	B-S	↓↓	↓↓	↓↓
	Enflurane	B-S, seizures	↓↓	↓↓	↓↓
	Sevoflurane	B-S, seizures	↓↓	↓↓	↓↓
	Desflurane	B-S	↓↓	↓↓	↓↓
	Barbiturates	B-S, epileptiform patterns	↓↓	↓↓	↓↓
Alpha 2 agonist	Clonidine	Slow	↓	?	↓
	Dexmedetomidine	Slow	↓	?	↓
NMDA antagonist	Nitrous oxide	Frontal beta	↓↓	–	↓↓
	Ketamine	Theta	↑	–	↓
	Xenon	Central slow	↓	↓	↓
Slow wave sleep		Spindles, vertex-wave	↓	↓	↓

Summary of neurophysiological effects of hypnotics in monoanesthesia at surgical level, that is, 1 MAC (minimal alveolar concentration) or higher for volatile anesthetics. Slow wave sleep is included for comparison, as the EEG patterns and effect on somatosensory and motor responses of specific γ-amino butyric acid ($GABA_A$) agonists and alpha-2 agonists are probably caused partly by the same mechanisms. On the other hand, arousal changes all these neurophysiological measures towards awake patterns, although we only wake up from physiological sleep. Somatosensory evoked potential (SEP) refers mainly to the short latency cortically generated waves and mid-latency auditory evoked potential (AEP) mainly to cortical mid-latency auditory evoked potentials. B-S, burst suppression.

recording and stimulation, such as different stimulus parameters (rate or ISI with SEPs) and voltage numbers, and intervals between pulses in tcEMEP stimulation. When these do not give satisfactory results, different anesthetic agents may be tried, such as changing from inhalational agents to TIVA.

Many monitoring devices allow continuous monitoring of the EEG which gives an additional view of cerebral function. The univariate measures such as BIS, the detection of EMG activity, and identification of the fortunately rare occasions of epileptiform activity or ischemia can be helpful companions to anesthesia and monitoring. By understanding the physiological and pharmacological basis of anesthesia and monitoring, the operating room team can considerably improve the safety of the patient.

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