Electrical Activity of the Brain in Relation to Anesthesia

Hiroshi TAKESHITA
Department of Anesthesiology, Yamaguchi University School of Medicine, Ube
Haruka ASARI
Department of Anesthesiology, Kyoto University Hospital, Kyoto, Japan
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A general anesthetic state can be achieved only by the penetration of anesthetics into the brain. However, there is no simple theory explaining the mechanism of the anesthetic state that fits all the observed facts and is universally acceptable. Although neurophysiological study itself is not capable of ascertaining the exact nature of anesthesia, it is one very useful to explore the anesthesia mechanism because electrical activity of the brain is a reflection of cerebral functions and metabolism and has contributed to exploration of the complex neural mechanism of the brain, both in waking and sleeping states. Electrical activity of the brain, especially electroencephalogram which reflects electrical activity of the cerebral cortex and is more familiar to practicing anesthesiologists shows significant change under anesthetic state and abnormal physiological conditions in relation to anesthesia. In this paper electrical activity of the brain during anesthesia will be discussed and much emphasis will be placed on the effects of anesthetics on neural mechanisms which are important as neurophysiological basis of the electroencephalogram (EEG).

I. Neurophysiology and Neuropharmacology of EEG

1 Basic Consideration of EEG

Noraml spontaneous rhythm of EEG consists of alpha waves with a frequency of about 10 cps. When appropriate sensory stimuli, particularly visual stimuli in men, are applied, this alpha wave is replaced by beta waves with a frequency ranging from 14 to 25 cps. This phenomenon is well known as "alpha blocking" and has two different patterns. One is that both alpha and beta waves are depressed with relative predominance of beta waves which has not been evident in a resting state and the other is that alpha waves are depressed with actual enhancement of beta waves.[1] The alpha rhythm has a frequency ranging from 4 to 8 cps, and has a normal variation in amplitude in different normal persons. Normal basic patterns of EEG vary with difference of species, for instance the basic EEG pattern of a cat consists of 5, 6 cps waves. By convention, high-frequency (short duration) waves which consist of beta rhythms

are called "fast activity" and low-frequency (long duration) waves are called "slow activity" which involves theta rhythms, 4 to 8 per second and delta rhythms, below 4 per second. In general, the amplitude of the waves is inversely proportional to the frequency.

Although EEG reveals the electrical activity of the superficial layer of the cerebral cortex, there is some controversy regarding the elements of the electrical potential which may constitute EEG. The nerve cell is composed of the cell body, the dendrites and the axon which transmits excitation away from the cell body. The excitation of both cell body and axon is accompanied by a spike potential. In contrast, electrical discharge along the dendrite is a slow potential. These three components of electrical discharge in the nerve cell that is, the dendrite, the cell body and axon potentials are different from the postsynaptic potentials which are produced in the postsynaptic region by the chemical transmitter substances secreted from fine terminal branches of an axon. The postsynaptic potentials have long duration similar to the dendritic potential and are composed of inhibitory and excitatory potentials. The former hynerpolarizes the membrane of the synaptic region, but the latter depolarizes. It is generally accepted that the individual electric discharge of the EEG must be visualized not as spike potentials but as relatively slow alternations of dendritic[2] or postsynaptic potential.[3] Both of these have a duration of about 10 to 20 msec much longer than spike potential. In addition to this, either potential must be summated. Whereas the dendritic potentials may be propagated along the dendrite, the postsynaptic potentials do not propagate. Both potentilas do not obey "all or none" principle. At the present time, the postsynaptic potential is considered to be more important as an electrogenetic component of EEG than the dendritic potential.[4]

As to the relationship between the spike discharges of the cell units and the EEG, Li and Jaspers[5] could find no relation between them at least in the resting rhythm of the cat. However, Pollen et al[6] have found a closer relationship between unit discharge and slow wave in conditions where EEG is itself exhibiting marked rhythmicity. With increasing evidence that the EEG is a summation of excitatory and inhibitory postsynaptic potentials produced at different levels in the cortex, the importance of some phase relationship between unit discharges and EEG waves has now been recognized.

The synapse where excitation propagate from one neuron to the other, is most sensitive to the changes of internal and extenal milieu such as anesthesia, hypoxia, hypoglycemia, hypothermia. The axon is known to withstand adverse changes of milieu better than the cell body and dendrites. The postsynaptic potential which involves the activity of the latter structures is more susceptible to changes of milieu than the presynaptic potential consisting of electrical activity of the axon. Anesthetics depress the postsynaptic function sooner and more severely

than the presynaptic activity. However, there are some chemicals such as tubocurarine and strychinine which may enhance specifically the postsynaptic activity without markedly affecting the presynaptic potentials.[7]

2 Arousal response

The phenomenon similar to alpha blocking in men can be observed in experimental animals. When appropriate sensory stimuli are given to the animal who is drowsy or lightly anesthetiged and shows high voltage slow wave activity, the EEG is replaced by low voltage fast wave activity which lasts even after the cessation of the stimulation and appears over the wide area of the cerebral cortex. At the same time the animal awakens. Arousal response consists of EEG "activation" and the behavioral change from sleeping to waking. On the other hand, it is described as "deactivation" when the animal becomes drowsy and shows slower high voltage activity. Although slow high voltage activity is a synchronized pattern due to the synchronized activity of individual neural elements and fast low voltage activity is a dysynchronized pattern from the electroencephalographic standpoint, these words must be used for descirptive purposes. Usually EEG activation corresponds to arousal of behavior. However, in activated sleep EEG shows fast activity similar to the arousal pattern but, nevertheless, the animal is apparently asleep.[8]

The most important mechanism responsible for EEG activation and deactivation is the ascending reticular activating system. According to French et al,[9] the neural mechanism of EEG activation is in the brain stem reticular formation from where the centripetal pathway diffusely projects to the cerebral cortex directly or with relay in nonspecific thalamic nuclei. This system controls the appearance and maintenance of EEG activation. The reticular formation also has an ascending inhibitory system to the cerebral cortex which is cooperative with the activating system. In addition to this, the reticular formation has a descending system which modulates spinal activity by inhibitory and facilitatory influences. More important is the fact that the reticular formation is not able to drive itself but is driven by the inflow of peripheral stimuli and some chemical substances in the milieu,[10] so that it plays the part as modulator for the complex feed back mechanism of the central nervous system. For the sake of simplicity the role of the reticular formation is tentatively limited to the ascending activating system. An important source of neurons connecting with the reticular formation is known to be the spinal cord. These connections or collateral branches leave the main axon trunks of the brain stem. The classical sensory route through specific thalamic nuclei is called the specific or primary sensory pathway whereas a route through nonspecific thalamic nuclei is called the nonspecific or secondary sensory pathway. However, there is clear evidence that the ascending reticular activating system of the brain stem has extrathalamic routes to the cortex. This route passes directly from the subthalamus and hypothalamus into

the internal capsule. Thus, in a broad sense the secondary sensory pathway includes both thalamic and extrathalamic routes.[11]

Recent work suggests that the reticular formation may play a part as a modulator for the limbic system which is the phylogenetically older part of the brain. The ascending system which lies in the reticular formation and the tegmentum of the lower brain stem runs up through the hypothalamus and reaches the limbic system. In contrast to the reticular activating system to the neocortex, the hypothalamic activating system to the limbic system was extensively studied by Tokizane et al.[12] The inflow to the hypothalamus mainly consists of primitive and visceral sensations and activates the limbic system.
The electrical activity of the hippocampus which is a main part of the limbic system is strikingly different from that of the neocortex. The electrical activity of the hippocampus in a waking state consists of regular slow activity (4 to 6 cps in the cat) and this charatcristic pattern changes to irregular fast activity in a sleeping or anesthetic state.[13]

For quantitative determination of the arousal responses in the neo-and paleocortex, the threshold value to cause the change in EEG by high frequency stimulation to the activating systems must be measured. In general anesthesia, there is a failure of EEG arousal upon the direct excitation of the ascending reticular system of the brain stem. Kato and Yamamura[14] reported that the threshold of arousal response at the neocortex increased by 124 %, 192 % and 38 % in ether light (3–4 % in inspired mixture), ether deep (6–8 % in inspired mixture), and nitrous oxide (80 % in inspired mixture) anesthesia, respectively.
In halothane anesthesia, the threshold value of arousal response is also inereased with deepening anesthesia.

The hypothalamic activating system is studied by the same fashion of stimulating the hypothalamus which activates the limbic system. The threshold values at the hippocampus to change from slow regular high voltage activity to fast low voltage activity are measured with different anesthetics. Nitrous oxide has no significant effect on the hypothalamic activating system whereas ether and halothane depress it. Morphine or pethidine depress the limbic system more significantly than the neocortex.[15]

In summary, the threshold values of the arousal response both in reticular and hypothalamic activating systems is increased by general anesthesia, but there are differences with individual anesthetics and with depth of anesthesia. However, it remains unanswered why the reticular formation is vulnerable to all centrally acting anesthetics though there is no implication that the ascending reticular system is the only neural mechanism susceptible to anesthetic agents.

3 Recruiting response

The recruiting response is another neural mechanism which may contribute to rhythmicity and wave form both of normal EEG and of EEG associated with

anesthesia. It is the cortical response to thalamic stimulation which has been considered typical of the activity of the thalamic reticular system (a part of the reticular system) as distinct from the specific projection system. The cortical responses which follow repetitive stimulation of specific thalamic nuclei has been called augmenting response.

The typical recruiting response may be identified by the following characteristics.[16] Maximum responses are obtained only with repetitive stimulation at frequencies between 6 and 12 per second (low frequency), or at frequencies corresponding to the dominant spontaneous cortical rhythm of the animal. The voltage of recruiting waves increases progressively with successive repetitive stimuli to a maximum within the first three to six stimuli, with continued repetitive stimulation, after the initial increase in amplitude, there is a decrease in amplitude even though the stimulus remains constant. With continuous stimulation there is a regular and gradual spindle-like waxing and waning of amplitude of these responses in a manner similar to that seen for the spontaneous spindles. The recruiting wave is a relatively monophasic surface negative wave of about 30 to 40 msec in duration and the surface negativity usually has a latency of about 20 to 30 msec. Between recruiting and augmenting responses there are some fairly close similarities, but the augmenting response is of relatively short latency and is always composed of an initial surface positive rapid deflection followed by a more variable surface negative wave.

The reason that the recruiting response is considered one of the most important neural mechanisms in the cerebral cortex is based on the fact that these waves are very similar to the spontaneous spindle waves in regard to their appearance and distribution. In addition, it is noteworthy that the spontaneous spindles are readily obtainable in sleep and light anesthesia. As to the origin for such rhythmical electrical activity, there are two speculations. The first is that an intrinsic factor is proposed in the cerebral cortex where a prolonged, apparently recurrent, postsynaptic inhibition stops cell discharge for 100 msec and no driving mechanism is needed to dicharge neurons upon recovery to normal excitability, the second is that centripetal impulses from a subcortical structure like thalamus to the cortex have some rhythmicity.[17] Anderson and Eccles[18] recently formulated the hypothesis that a series of after discharges evoked by stimulus into the thalamus is generated intrinsically in the neuron and its phasing device is due to widely depressed inhibitory postsynaptic potentials that are generated through a recurrent pathway from axon collaterals.

The effects of anesthetics on the recruiting response have been studied. Nitrous oxide and deep ether anesthesia increase the threshold of recruiting response by 14 % and 111 %, whereas light ether anesthesia has no significant effect.[14] Very small doses of barbiturate enhances the recruiting response and also is capable of blocking arousal.[19] With halothane anesthesia, amplitudes of recruiting

responses are enhanced and the threshold reduced, at the light level, but amplitudes are noticeably decreased and threshold is raised with deepening of anesthetic level.[20] Usually recruiting responses, present in the awake animal, are abolished when it is altered by stimulation of the reticular formation and conversely become intensified with impairment of consciousness. These responses behave as though depression of activity in the reticular formation resulted in a release of the mechanism for their production.[21] From these studies differential actions of various anesthetics on these responses become apparent. Nitrous oxide and deep ether exerts a major depressant effect at the level of the midline thalamus, but not so with pentothal and halothane. Kato et al[14] speculated that the combination of nitrous oxide with light ether anesthesia is rational from the neuropharmacological stand point, if various sites of the brain or neural mechanisms must be "affected" for the establishment of surgical anesthesia. Because nitrous oxide depresses recruiting response and ether depresses the hypothalamic activating system without any significant effect on recruiting response. Such interpretation may be applied to the combination of nitrou oxide with halothane or barbiturate.

4 Evoked potentials

In contrast to the intrinsic or "spontaneous" electrical activities which do not require any particular stimulus to the nervous system for their appearance, evoked activities that appear from various functional area of the brain by stimulation of sense organs or of some point along the ascending pathways. The detection of electrical changes evoked in the cortex by stimulation of sensory systems is always made difficult by the pressnce of continuous, spontaneous electrical activity of the cortex. A method to overcome the difficulty of detecting an evoked response against a background of spontaneous activity has been described by Dawson,[22] who used a system for recording successive sweeps of a cathoderay oscillograph. Exact synchrony of events was insured by trigger circuit locked to the sweep of the oscillograph. In this way, a deflection which consistently followed a timed impulse at a regular interval could be distinguished from random waves. This is also the earlier concept of averaging technique for research on evoked potentials. If one may assume that a response has a very similar or nearly the same wave form and latency for each stimulation, one may repeat the stimulus many times and by computation with a digital computer, one may obtain an average response.[23]

Further information on the anesthesia mechanism can be obtained with this technique and some results from animal experiments will be disscused here. The response of rabbits' visual cortex to photic stimulation once per second are produced by 100 flashes. In this situation the nomenclature applied to the various waves may be arbitrary. Evoked response taken from the visual cortex of the rabbits consists of a series of deflections which may last at least 800

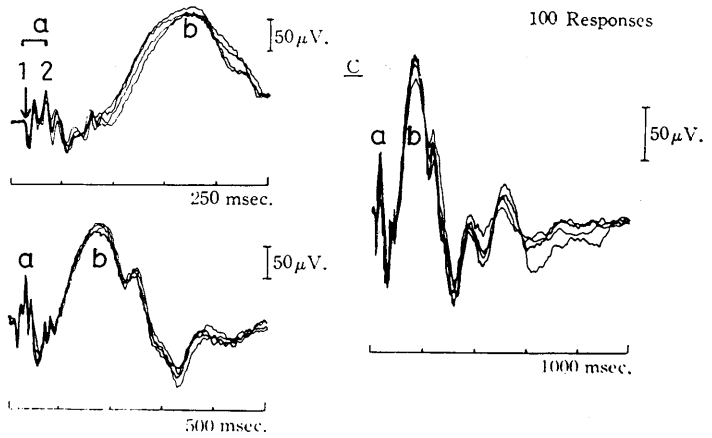
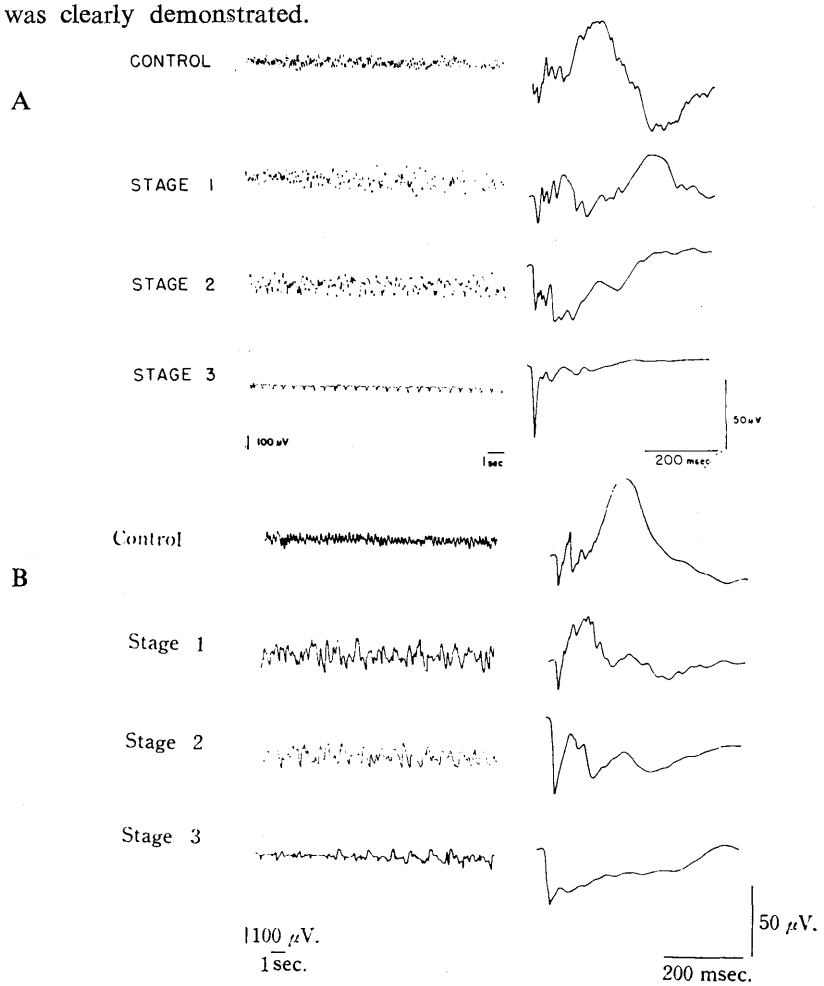


Fig. 1. Averaged photic response in rabbits. A, B and C are taken at various sweep ; 250 msec., 500 msec. and 1000 msec. respectively. Each of them consists of four averages (100 responses each). The first surface positive (downward) deflection is component 1. Following surface negative (upward) deflection with ripples is component 2. The 'a'-wave consists of component 1 and 2 and followed by a large slow negative deflection named 'b'-wave.

msec as shown in Fig. 1. Considering the first 250 msec of the response pattern in detail, the first surface positive deflection (Component 1 of the 'a'-wave) almost invariably begins approximately 14 msec after the flash. Component 1 is followed by surface negative deflection (Component 2 of the 'a'-wave) which usually has three or four ripples and persists 40 to 60 msec. Component 2 of the 'a'-wave, is followed by large slow and variable diphasic deflection ('b'-wave), swinging positive and then negative. The 'b'-wave is accompanied by repetitive discharges which have decreasing amplitude and finally become indistinguishable. Although the physiological mechanism of these waves still remains obscure, component 1 may be the sign at the pial surface of impulses that have travelled through the relays of synapses in the optic thalamus. This deflection also has been interpreted as postsynaptic potential which is produced in the synaptic region of the pyramidal cell body, although some investingators refer this, at least in part, to presynaptic potentials.[24] Component 2 is regarded as the electrical concomitants of discharging cortical neurons, and composed of postsynaptic potentials in axo-dendritic synapse or potential gradient travelled along the apical dendrites. Component 2 may be modified by the arrival of impulses in the non-specific afferents which make axo-dendritic connections in the more superficial layers of the cortex and its ripples may represent the signs of serially approaching impulses to the cortex via fibres with different conduction velocity or different multisynaptic relays.[25] A 150-300 msec negative potential which is called the 'b'-wave is a prominent feature of the cortical response to stimulation at the retina or the optic nerve.[26] Such slow potentials are common

to all evoked cortical potentials[27] and are very susceptible to continued flashes, anesthesia and hypoxia in the rabbit.[28]

Fig. 2 shows the effects of three different anesthetics, pentothal, halothane and ether, on averaged evoked potentials. Three stages are classified according to the change of EEG and averaged evoked response. Although the over-all change of averaged evoked response with deepening of anesthesia showed a very similar pattern by three anesthetic agents, the 'b'-wave is more susceptible to anesthesia than any other part of the response. The depression of 'b'-wave was accompanied by enhancement of component 2 of the 'a'-wave in halothane and pentothal, but not with diethyl ether. Component 1 was usually enhanced by halothane and pentothal, but not with ether. In deep anesthesia the averaged evoked response only showed component 1 because it was more resistant to anesthesia than any other components. From these experiments, the difference of averaged evoked response pattern between ether and halothane or pentothal was clearly demonstrated.



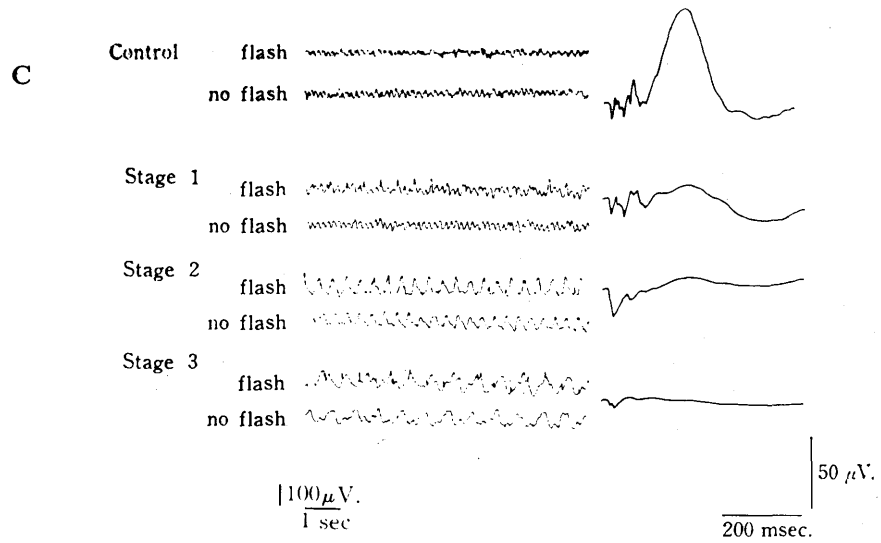


Fig. 2. EEG and averaged evoked response by flash during anesthesia. Three stages are classified according to the change of EEG and averaged evoked response patterns. A, Pentothal; B, Fluothane; C, Diethyl ether.

5 Single units activity

All results mentioned above were obtained with microelectrode technique. Electrical activity of the brain studied with this technique must be either summation or average of electrical potentials in innumerable neuronal and glial elements. In contrast to this, it is important to study the electrical activity of the brain with microelectrode technique which makes possible extracellular unit spike recordings for prolonged, systemic observation of unit activity of the brain.

From the studies with microelectrodes, single unit activity of the mesencephalic reticular formation appears to be suppressed in anesthetic state. Shimoji and Bickford[29] demonstrated that anesthetic agents irrespective of their kind produce suppression of spontaneous firing activity, but susceptibility of units to anesthetic agents vary widely from unit to unit. There are two types of change in spontaneous firing patterns produced by anesthetics, namely the "grouping" and the "tonic type" as shown in Fig. 3. The former is seen more often during pentothal and halothane whereas the latter is more characteristic of ether. Their observations indicate the extreme complexity of neurophysiologic changes which form part of the so-called anesthetic state and both excitatory and inhibitory influences are active and there are complex changes in the patterning of unit firing.

Yamamoto et al[30] studied the effect of barbital on evoked and spontaneous activity in a single unit of the sensorimotor cortex and mesencephalic reticular

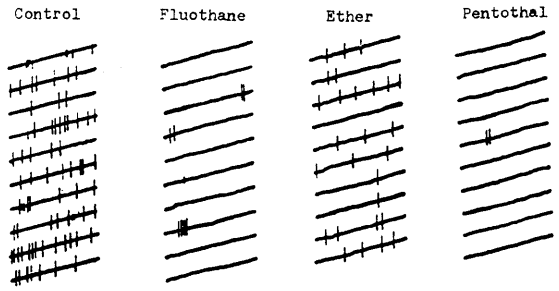


Fig. 3. Spontaneous firing patterns of one midbrain reticular formation unit exposed to different kinds of anesthetics (29), "Grouping pattern" is seen more often during fluothane and pentothal. "Tonic pattern" is more characteristic of diethyl ether. 1 sweep=200 msec.

formation. In both sites, single unit activity is depressed, but the evoked activity is more resistant to anesthesia than the spontaneous activity. As to the evoked potentials, the unit firing with longer latency is more susceptible to anesthesia than that with shorter latency.

Therefore, there seems to be little uniformity in the effect of anesthetic agents and thus little basis for a simple neuronal model of the anesthetic state such as perphaps would be suggested by the classical works.

II EEG pattern produced by anesthetics

1 Continum of cerebral depression

EEG during administration of various anesthetics shows significant changes in its frequency and amplitude. Since Courtin, Bickford and Faulconer[31] reported their classical work on electroencephalographic classification of anesthetic depth in 1950, electroencephalographic effects of the commonly used anesthetics have been described by a number of investigators. However, the work by the Mayo group is considered to be a milestone in electroencephalography in relation to anesthesia.

In this paper, it is not necessary to describe the changes in frequency and amplitude of electrical activity during the administration of various anesthetics. The readers may be refered to various books and reviews.[32][33][34]

As to the classification of electroencephalographic pattern during anesthesia, the following should be recognized. First, encephalographic level is better classified with commonly used signs of anesthetic depth, such as blood pressure, pulse rate, respiratory movement, eye movement, muscle relaxation and other reflexes. Secondly, reviewing the classification of EEG pattern, there are variations of investigator's choice of what constitutes recognizably different patterns which another investigator's might classify as a transition. Thirdly, the anesthetic concentration in inspired gas mixture and speed of induction may modify the

persistence of a particular electroencephalographic level. Finally the toxcity and potency of individual agents should be evaluated in considering the continum of cerebral depression. It is well known that nitrous oxide is not capable of producing burst suppression and halothane causes a significant fall of blood pressure when it is administered until severe cortical depression is seen in EEG.

From the descriptions of electroencephalographic levels during the administration of various anesthetics, one may readily visualize a sequence of events as a continum of cerebral depression which is typically shown with diethyl ether by Courtin et al. They described a general basic pattern as follows. Early in the variations from normal comes an increase in frequency to 20 to 30 cycles per second. As consciousness is lost, this pattern of small rapid waves is replaced by a large (50 to 300 microvolts) slow wave (1 to 5 cycles per second) that increases in amplitude as it slows. The wave may become irregular in form and repetition time. The amplitude next begins to decrease, and periods of relative cortical inactivity (the so-called burst suppression) may appear until the depression finally results in the entire loss of cortical activity and a flat or formless tracing. The Mayo group classified the grade of burst suppression according to the duration of electrical silence and there is a progressive decrease in amplitude of the burst as the duration of electrical silence increases.

Frequency analysis is of great assistance to describe this continum of EEG changes. If EEG frequencies which make up the EEG are divided into seven bands, namely, β_3 (60–30 cps), β_2 (30–20 cps), β_1 (20–12 cps), α (12–8 cps), θ (8–4 cps), δ_1 (4–2 cps) and δ_2 (2–1 cps), the high frequency bands are prominent in light anesthesia. With increasing doses of the anesthetics agent, low frequency bands become increasingly prominent and may disappear in very deep anesthesia. Fig. 4 shows the changes of integrated voltage in an arbitrary unit of each band during halothane anesthesia in man. When an integrator with frequency analyzer is used more information will be available. Intagrated cortical output which is the function of the amplitude and persistence of EEG, but does not necessarily represent energy output of the brain reaches its peak during relatively light level of anesthesia. With increasing doses of anesthetic agent, it becomes increasingly suppressive in its effect on electric output until finally, in very deep anesthesia, all electrical activity disappears. These over-all changes in "integrated voltage" shown in Fig. 5 provide a good understanding of electroencephalographic sequence during anesthesia, although there is some deviation of the continum of the EEG changes from a general pattern according to individual anesthetic. Although the integrated voltage does not directly represent the energy output of the brain as mentioned above, its increase during relatively deep anesthesia seems to be paradoxical. In order to solve this paradox D.C potential must be taken into acount[35]. As the D.C potential which is the potential too slow to be recorded by routine instruments decreases with anesthesia, the net energy output of the

brain must be decreased with deepening of anesthesia.

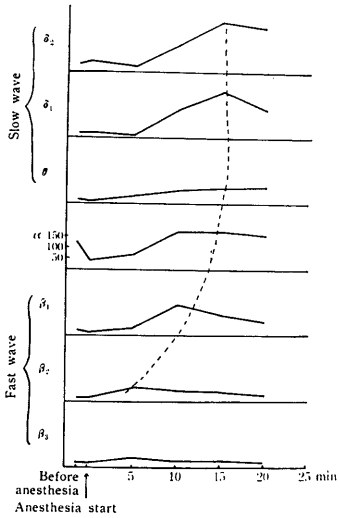


Fig. 4. The change of "integrated voltage" of each frequency band during Fluothane anesthesia in man. Dotted line connects the peaks of β_3 to δ_2 band.

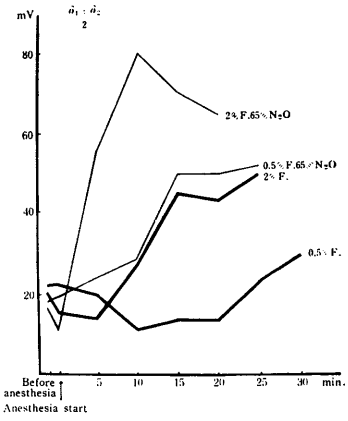


Fig. 5. The change of "integrated voltage" of δ band in nitrous oxide and Fluothane anesthesia in man. Variations in "integrated voltage" of δ band during 0.5% Fluothane and 65% nitrous oxide anesthesia are similar to those of 2 % Fluothane.

2 EEG level and anesthetic concentration in the blood

Faulconer[36] found that the linear correlation between their encephalographic levels and arterial concentration of diethyl ether in man. Succeeding studies confirmed their conclusion, and a dose-response relationship has been established for most of the commonly used anesthetic drugs. Faulconer also showed that a concentration of nitrous oxide in excess of 10 mg per 100 ml of blood reduced the amount of ether needed to reach a given electroencephalographic level of anesthesia. Fig. 6 shows the effects of combined use of nitrous oxide with halothane on electroencephalographic level by frequency analysis. The output of δ band is represented as $\frac{\delta_1 + \delta_2}{2}$ and as an index of the changes in anesthetic depth with time. As clearly shown in the figure, the addition of 65% nitrous oxide to 0.5 % halothane produces a marked slowing effect on the EEG as compared to 0.5 % halothane alone, and shows almost the same electric output of δ band as that of 2 % halothane.

The concentrations of ether or cyclopropane in plasma[37] corresponding to each different electroencephalographic pattern are reproducible and vary little

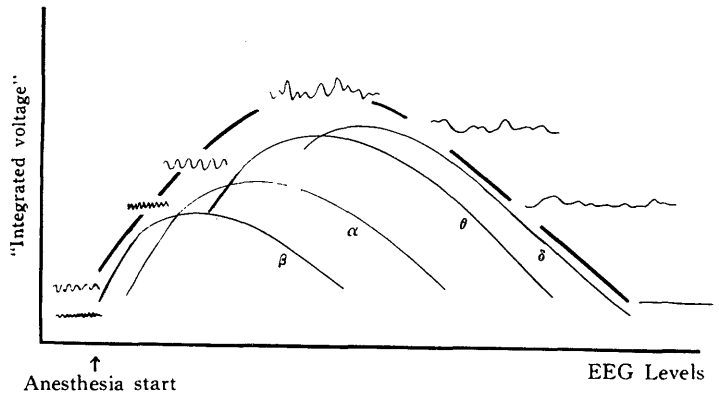


Fig. 6. Relationship between EEG levels and "integrated voltage", modified from Faulconer and Bickford. (Electroencephalography in Anesthesiology, Faulconer, Albert, Jr., Bickford, Reginald, G., Springfield, Charles C Thomas, 1960) β, α, θ and δ indicate "integrated voltage" obtained by integrator in an arbitrary unit. See text for details.

from patient to patient. Wolfson et al[38] described four patterns during methoxyflurane anesthesia depending on the presence or absence of theta waves, delta waves or burst suppression and found a linear relationship between the average blood levels at which successive EEG patterns appeared. Brand et al[39] found that with thiopentone there is relatively little connection between EEG patterns and plasma drug level. Inspite of the plasma concentration of thiopentone tended to rise successively high, especially after the first hour, EEG pattern and clinical depth of anesthesia remained constant. This fact appears to be due to a form of acute tolerance to the drug. They proposed a true tissue adaptation which is still undetermined, upon prolonged exposure to thiopentone. In this way, the central nervous system develops resistance to the depressant effects of the drug. It has not been determined whether or not such a tissue adaptation occurs with volatile anesthetics.

3 Evoked potentials in humans during anesthesia

As mentioned in the previous chapter, evoked respone can be recorded via scalp electrodes. For the anesthesiologist it is of prime importance to study the pharmacodynamics of anesthetics on the central nervous system of man. Among the sensory modalities vision is well represented and electrical activity from this stimulus can easily be monitored, therefore visual stimulation by a flash of light is especially suitable as a means of studying more objectively the effects of anesthetics on sensory input in man.

Along this line, Domino[40] studied the effects of preanesthetic and anesthetic drugs on the averaged evoked potentials. Nitrous oxide was relatively ineffective in depressing the responses and occasionally enhanced the 'primary' complex.

Diethyl ether and cyclopropane both of which readily causes slow wave activity in clinical anesthetic concentrations were especially effective in depressing the response. On the other hand halothane or methoxyflurane which maintain fast activity at the clinical anesthetic depth did not completely obliterate the averaged evoked response, but enhanced the 'secondary' complex.

A similar study of auditory stimulation was also carried out in this laboratory. Among the sensory modalities pain and hearing may be of utmost importance for the anesthesiologist. Auditory stimulation consists of clicks generated by stimulator feeding into two tightly fitting earphones. The results were similar to those reported by Domino in spite of the difference of sensory input. As shown in Fig. 7 nitrous oxide did not significantly alter the averaged evoked response by click. Nitrous oxide-oxygen-ether anesthesia depresed the response. With pentothal and halothane, the wave form of averaged evoked response are very similar and changed as anesthesia deepened to that with large surface positive deflection.

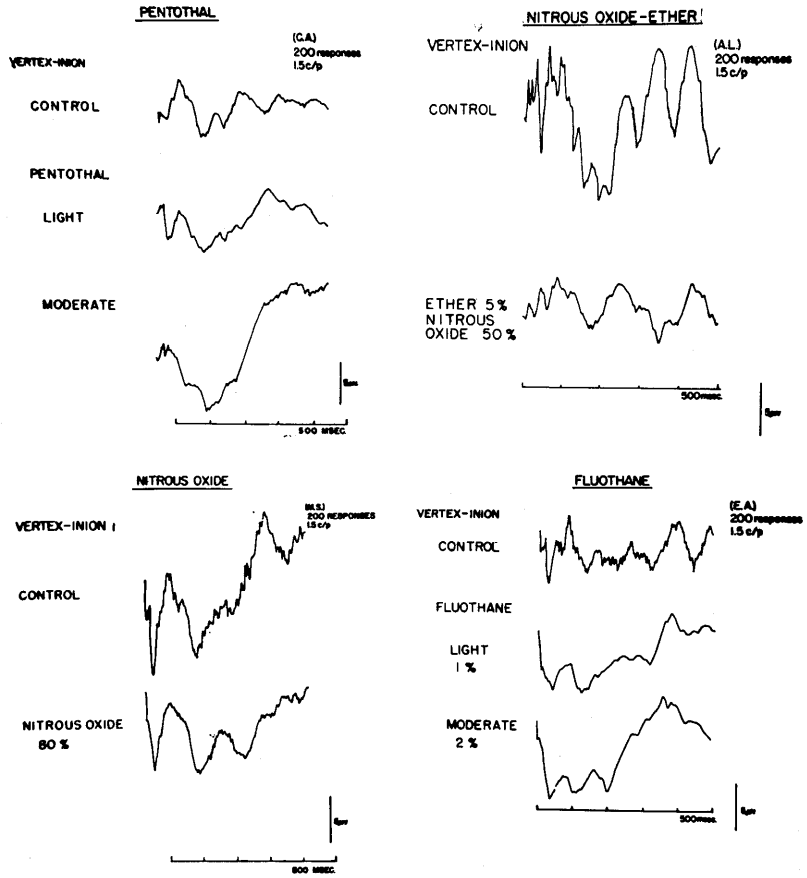


Fig. 7. Averaged evoked response by click in anesthetized man. Responses were obtained from vertex-inion lead.

As to the electrogenesis of the evoked potential, there is no systemic and sufficient study on the cellular basis of the evoked potential. The explanation of electrogenesis of evoked potential presented in the photic evoked response in animals may be restricted to the visual pathway and not based on cellular basis. Fox et al[41] showed a close relationship between the intracortically recorded evoked potential and the activation cycle of some cells or fibres recorded with the same electrode. Recently, the some relationships between the intracellularly recorded synaptic activity of cortical cells and the surface potential in the sensori-motor cortex after electrical stimulation of the thalamus and synaptic activity in the visual cortex after electrical stimulation of the optic tract were demonstrated. Thus, Creutzfeldt [42] concluded that evoked potentials are composed of compound excitatory and inhibitory postsynaptic potentials of cortical cells as well as of synchronous afferent and efferent fibre activity and the waves which swing to negative direction may represent an excitation of most cortical cells and a polarization (inhibition) will be present during the waves which swing to positive direction.

It is unfortunate that the significance of the averaged evoked response in man is not fully undestood having limited clinical value. However, it is clear that during general anesthesia a great deal of sensory input is reaching the cerebral cortex and very deep general anesthesia in halothane and methoxyflurane which might cause severe circulatory depression is only capable of abolishing the evoked response in the cortex.

SUMMARY

Electrical activity of the brain was discussed with special reference to electroencephalogram which is very familiar to anesthesiologists. The electroencephalogram records the electrical activity of the cerebral cortex which is mainly composed of dendritic or postsynaptic potentials. The differential effects of anesthetics on the electrical activity of the brain stem and thalamic reticular systems were clearly demonstrated. Commonly used general anesthetics depressed the ascending reticular activating system and hypothalamic activating system, but the degree of depression varied with individual anesthetic and with depth of anesthesia. The effect of anesthetics on the thalamic reticular system was studied in relation to recruiting response. Nitrous oxide and deep ether have a depressant effect at the level of the midline thalamus, but this is not so with pentothal and halothane. The study on evoked response also showed differential action of various anesthetics, although the electrogenesis of the evoked potentials awaits further study. From the study with microelectrodes, it has become apparent that the so-called anesthetic state is composed of extremely complex changes in

the patterning of unit firing and there is little uniformity in the effect of anesthetic agents and thus little basis for a simple neuronal model of anesthetic state.

The continum of cerebral depression produced by anesthetics was described and its generalized pattern was well recognized. The use of frequency analyzer and integrator provided more quantitative description of the electroencephalographic pattern during anesthesia. Although there is some controversy, the dose-response relationship between electroencephalographic levels and anesthetic concentration in the blood was found in common anesthetic agents. The averaged evoked potentials obtained during clinical anesthesia revealed that a great deal of sensory input is reaching the cerebral cortex and deep halothane anesthesia which might cause severe circulatory depression is only capable of abolishing the evoked response in the cortex. As to the effect of general anesthetics on the electrical activity of the brain, a common pattern can be drawn, but there are considerable differences between the anesthetics in their effects on the different neural mechanisms.

The computer technique in neurophysiological study is a powerful addition to simple multichannel recording and might be used over a wide range to search for the action of anesthetics in various part of the brain. Hopefully, this presentation will, in some degree, advance current understanding of neurophysiological basis of the anesthetic state and will bring the disciplines of neurophysiology and anesthesiology more closely togerher.

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