EFFECTS OF DRUGS ON THE ELECTRICAL ACTIVITY OF THE BRAIN: ANESTHETICS

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The emergence of the newer anesthetics such as ketamine and enflurane tested the concept that all anesthetics are depressants. It was with this in mind that the editors requested this chapter, which reviews neurophysiological studies mainly in cats that collate the various states induced by the anesthetics into an organized schema. I apologize to those readers who expected a broader review of the anesthetic state and/or a less biased approach. On the other hand, I hope that this review serves as a focus for the reorganization of our concept of anesthesia and its relation to other drug-induced states.

INTRODUCTION

Both basic scientists and clinicians tend to consider a subject asleep or anesthetized when lying down and hyperexcited when moving around. This view is only partially correct. In the hyperexcited, cataleptic, and preconvulsant states, subjects are immobile but their CNS is highly activated. We often cannot determine either the behavioral or functional brain state of subjects by mere observation. The loss of righting reflex, as the classic pharmacological test for determining CNS depression, sleeping time, or anesthesia time, is misleading since this tests only for immobility and not for the functional activity of the CNS. To determine the state of consciousness of a subject, it is necessary to examine the level of excitability of the brain. By placing electrodes in various parts of the brain and examining the brain wave activity during various states of normal behavior, such as wakefulness and sleep, and during drug-induced states, the effects induced by these states on CNS activity can be interpreted (1–3).

This presentation attempts to correlate some of the acquired data into a meaningful interpretation of the action of the CNS anesthetics.

Agents used as anesthetics form a diffuse group which are generally classified as CNS depressants (4, 5). Pharmacologists often view anesthesia as a progression of decreasing CNS irritability leading to depression and finally death (Figure 1). In contrast, increasing states of irritability represent an opposite continuum leading to hyperexcitation, convulsions, and finally death (6). The progressive depression induced by the anesthetic agent diethyl ether was fitted into a schema by Guedel (7). The schema implies a progressive decrease in CNS excitability (Figure 1) as follows: stage I, analgesia; stage II, delirium; stage III, surgical anesthesia; and stage IV, medullary paralysis.

The first two stages of anesthesia, however, are characterized by motor excitation and ataxia in stage I, and hallucinatory and cataleptoid behavior in stage II. These two stages constitute a stage of excitation or increased stimulation rather than CNS depression (4, 8–10). Ataxia is considered, by some, to imply CNS depression; however, it actually indicates an inability to coordinate motor activity. The ataxia

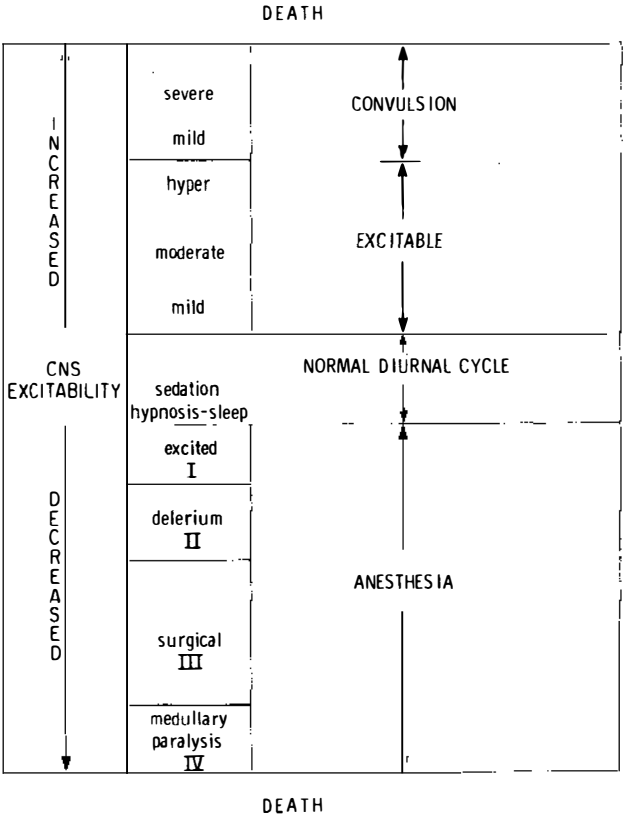

Figure 1 Classical unidimensional schema of CNS excitation and depression (29).

that appears during stage 1 anesthesia is correlated with elevated levels of neuronal activity, not depression (4, 5).

In addition, prior to clinical trial, both diethyl ether and nitrous oxide were well-known nonmedically as stimulants, euphoriants, and hallucinogens (11). Likewise, other anesthetics have confusing histories. α-Chloralose has been described as a convulsant-anesthetic agent (12), is often used in animals as an anesthetic for neurophysiological studies (13), and was used clinically to activate the electroencephalogram (EEG) of suspected epileptic patients (14). γ-Hydroxybutyrate (GHB) was reported to be a possible neurotransmitter in sleep (15) and also was utilized as an anesthetic in several thousand neurosurgical patients (16). Several investigators reported (16–18) a similarity in EEG activity between anesthetic doses of GHB and pentobarbital. However, subsequent studies demonstrated that GHB (2, 19, 20) has behavioral and neurophysiological properties distinctly different from those of pentobarbital and, in fact, in high doses is a convulsant.

Phencyclidine (Sernyl®) was introduced as an anesthetic in clinical trials in 1957 (21, 22). This drug induced amnesia, analgesia, catalepsy, anesthesia, and convulsions as well as profound postoperative delirium and acute psychotic reactions which prevented it from being accepted as an anesthetic in man. It is presently used widely in veterinary medicine as an immobilizing agent for short surgical procedures. In addition, this agent is used widely as a street drug (23), called PCP, Peace, Angel's Dust, Horse Tranquillizer, or Hog. A less potent derivative of phencyclidine, ketamine, with similar properties is used as an anesthetic mainly in the young or elderly and less frequently in young adults for limited surgical procedures. Domino et al (24) performed a controlled study of ketamine in twenty adult volunteer prisoners. He found ketamine to be less potent than phencyclidine; it did not induce convulsions, but did induce analgesia and anesthesia. The principal disadvantage of ketamine was its adverse psychic effects during emergence, such as hallucinations and changes in mood, body image, and affect, some of which were so frightening to some of the subjects that they preferred not to repeat the drug. Domino et al noted that in some subjects, ketamine induced an alarming rise in systolic and diastolic blood pressure and heart rate, along with sweating, lacrimation, hyperactive tendon reflexes, and a rise in blood glucose levels. In addition, during the catalepsia many of the protective reflexes, such as laryngeal, pharyngeal, eyelid, and corneal, were maintained. EEG studies in these volunteers demonstrated a hypersynchronous slow-wave pattern during catalepsia. To date there are no reports of significant street abuse of this drug.

Enflurane (Ethrane®) is a gaseous anesthetic with properties similar to those of ketamine (25) but is more efficacious in terms of CNS excitation in that it readily induces seizures at doses slightly higher than those that induce anesthesia (26). The close association of some anesthetic agents with states not usually considered to represent anesthesia, such as seizures and street abuse to induce hallucinations, suggests that we must alter our pharmacological concept that there is a stereotypical anesthetic state characterized by CNS depression. For a review of the neurophysiology of anesthesia see references 27–29. We later look further into the characterization of the anesthetic state but first look at some concepts of the functional

organization of the CNS. In 1951, Himwich (30) developed the concept of horizontal levels within the brain that were reversibly affected sequentially by increasing depths of anesthesia. As the subject progresses through the various depths, the cerebral cortex is depressed before the subcortical diencephalon, then the mesencephalon and pons are gradually depressed, and finally deepest anesthesia occurs when the vital centers in the medulla are depressed.

More recent developments in neurophysiology have given strong support for an alternate concept of CNS function and drug action. Rather than horizontal stratification of the brain, Livingston (31) visualized the CNS as composed of three highly interrelated but vertical systems: the specific sensory, the nonspecific sensory, and the motor system. The nonspecific sensory system is seen as responsible for interrelating and modulating all sensory-motor interrelationships. This nonspecific system is located essentially within the midline structures, running from the medulla up to the diencephalon, and contains the ascending reticular activating system described by Moruzzi & Magoun (32). Since the reticular formation was demonstrated to be a vital system for the control of wakefulness, several investigators have attempted to relate both sleep and anesthesia to altered functioning of this reticular system. The reticular formation is very sensitive to changes in the spontaneous wake-sleep cycle (3) and is likewise sensitive to states induced by various anesthetics (33–36).

CONTINUUM OF STATES

Based on the results of neurophysiological studies of anesthetics, excitatory, hallucinogenic, and convulsant agents in cats, Winters et al (4, 5) proposed a multidirectional schema of the progression of states of CNS excitation and depression to replace what was implied in the unidirectional schema of Guedel (7). The schema (Figure 2) states (5) that anesthetics and CNS excitants induce an initial excitation (stage I) characterized by increased motor activity including ataxia. Some anesthetics then bypass stage II and directly induce surgical anesthesia (stage III) characterized by a loss of responsiveness to stimuli, slow regular respiration, and CNS depression. Other anesthetics induce stage II prior to stage III. Stage II is characterized by bizarre postures and inappropriate behavior—hallucinatory (*A, B*) and cataleptoid (*C*). During stage II-C, as in stage III, the subject is relatively unresponsive to stimuli. Many anesthetics do not induce stage III following II but either induce only stage II or progress to heightened levels of CNS excitation, i.e. myoclonic jerking followed by generalized seizures. Further CNS depression during stage III will progress to stage IV (medullary paralysis) with depressed respiration and/or cardiovascular function terminating in death. During stage II and myoclonus, the respiratory and cardiovascular systems are not depressed and may be markedly stimulated. Both progressions are reversible, providing the subject does not die from respiratory and cardiovascular collapse either during the convulsions or stage IV.

Both the arousal response to stimuli and the righting reflex are absent during stage II-C and stage III. Thus, behaviorally it is difficult to differentiate between these two divergent states.

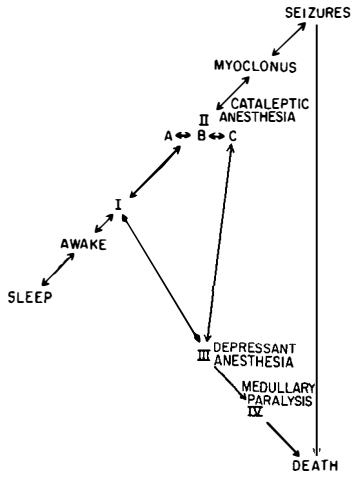

Figure 2 Schematic representation of the stages of anesthesia. Stage I, II, III, and IV, myoclonus, seizures, and death are shown. CNS excitation is implied above the awake level and CNS depression below.

In a recent review, Winters (37) discussed in detail the induced behavior and neurophysiology of the states of CNS excitation including stage I, II-A, II-B, II-C, myoclonus, and seizures; the induction of these states by various drug types, i.e. anesthetics, hallucinogens, and convulsants; and the progression of loss of awareness and recall during stages II-A, -B, and -C. Briefly stage II-A is characterized as a hallucinatory state identical with the state induced by hallucinogens or subconvulsant doses of pentylenetetrazol. Stage II-B and II-C are further progressions of this behavior with increased immobility and fixed postures characteristic of catalepsy. Stage II-A is related to a level of consciousness in which the subject is aware of and can recall the bizarre experience; while in stage II-B the subject is not aware but has recall; and while in stage II-C the subject is not aware and does not have recall. Descriptions of bizarre experiences following anesthesia are likely related to experiences recalled during emergence back to consciousness from II-C through II-B, II-A to stage I.

EEG

The characteristic electrical patterns of the EEG during the various drug-induced stages of CNS activity help to distinguish the divergent states of CNS activity. In cats (5, 8, 38) these patterns (Figure 3) are as follows: during stage I the mesodiencephalic and cortical EEG consists of an activated pattern with high frequency, low voltage wave-form activity (desynchronization). During stage II, the initial phase, A, is characterized by intermittent bursts of high amplitude 2.5 Hz waves (hypersynchrony) associated with hallucinatory behavior. During II-B the hypersynchronous waves are continuous and the bizarre actions of the cats are more intense. During

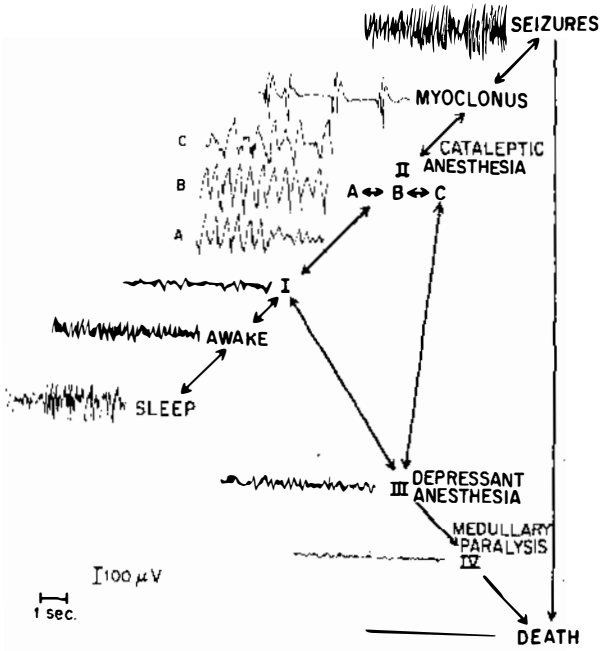

Figure 3 The cortical EEG (cat) representative of each stage is depicted. (See Figure 2.)

II-C the animals lose the righting reflex and maintain abnormal, bizarre postures that are cataleptoid and their EEG pattern changes to 1.5 Hz slow waves with occasional spiking. More profound CNS excitation is characterized by spontaneous and stimuli-induced myoclonic jerking and concomitant 400–500 μV large amplitude spike bursts followed by increasingly prolonged periods of relative electrical silence. This phase can continue or culminate in a generalized tonic-clonic seizure with high frequency, high voltage EEG discharge in all leads lasting as long as one minute. On the other hand, during stage III the general pattern is not as stereotyped as it is for the continuum of CNS excitation; there is a mixture of 10–12 Hz spindle-like bursts and irregular high amplitude slow waves. As anesthesia deepens the amplitude of the spindle bursts and slow-wave activity between bursts become progressively smaller until the burst suppression phase is reached. At this time the animal is unresponsive to all stimuli and has marked muscle relaxation. During burst suppression the spike bursts do not usually exceed 50 μV in amplitude, there are no after bursts, and the low amplitude spikes do not change in response to tactile or sensory stimuli. The intervals of isoelectric activity are progressively prolonged as the amplitude of spike bursts is reduced until the EEG is totally flat in deepest anesthesia. During emergence, each of the preceding EEG patterns reappear but are not as clear-cut as during induction.

GROUPING OF ANESTHETICS

Four general groups of anesthetic agents can be described according to the schema of the continuum of anesthetic states (Table 1). The first group of compounds is characterized by diethyl ether, which induces stage I and II and then progresses to stage III and IV. The second group includes nitrous oxide, trichlorethylene, and ketamine. These agents induce stage I and then stage II anesthesia but do not progress to stage III. While they do not usually induce seizures these agents may manifest generalized seizures if large doses are administrated. The third group is composed of phencyclidine, γ-hydroxybutyrate, α-chloralose, and enflurane. These agents induce stage I and II, then myoclonus and/or generalized seizures. The fourth group includes the barbiturates, halothane and methoxyflurane. These agents induce an initial stage I, followed by stage III, but do not manifest stage II activity. Higher doses induce stage IV medullary depression.

RETICULAR FORMATION MULTIPLE UNIT ACTIVITY

Reticular formation neuronal activity is an important control mechanism for the various states of wakefulness, sleep, and anesthesia. Studies were performed (3, 8, 38) utilizing the technique of continuous reticular multiple unit recording in intact freely moving animals. The multiple neuronal activity of the reticular formation during these various stages correlates with the EEG and behavior (Figure 4). During stage I the tonic activity of the reticular units is slightly increased over the awake control. During stage II, the excitability is equal or slightly greater than stage I. During myoclonus (spiking) and generalized seizures the intermittent neuronal activity is more profound and neuronal excitability is markedly increased. In contrast, during stage III the neuronal activity is markedly reduced and the neurons are relatively nonexcitable. The significance of these findings is discussed after a review of the actions of anesthetics on auditory evoked responses.

Table 1 Grouping of anesthetics according to induced stages

Drug	Anesthesia stage
Diethyl ether	I ⟷ II ⟷ III ⟷ IV
Nitrous oxide	I ⟷ II
Trilene®	
Ketamine	
Phencyclidine	I ⟷ II ⟷ seizures
γ-Hydroxybutyrate	
α-Chloralose	
Enflurane	
Barbiturates	I ⟷ III ⟷ IV
Halothane	
Methoxyflurane	

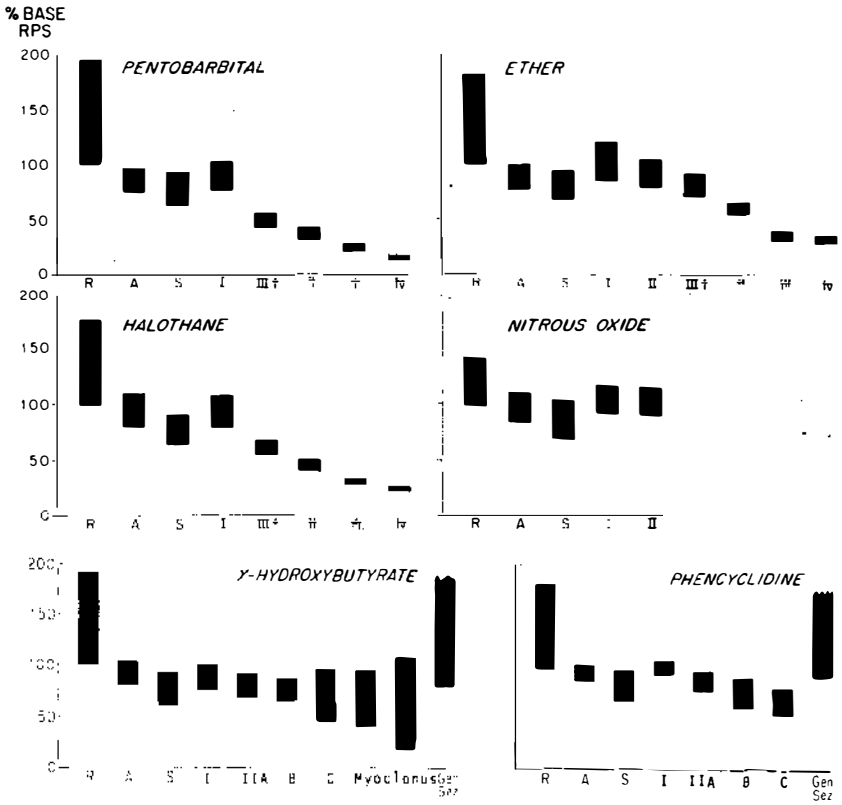

Figure 4 Bar graphs representing reticular neuronal activity during dream sleep (R), wakefulness (A), and spindle or slow wave sleep (S), and the various stages of CNS excitation (I, II, myoclonus, and generalized seizures) and depression (III, i, ii, iii, and iv). The height of the bar indicates neuronal excitability. [For details see method section (3).] [Modified from (8).]

AUDITORY EVOKED RESPONSE (AER)

A further evaluation of the excitability of the CNS is demonstrated by the studies on the averaged evoked response to auditory stimuli. The basis of these studies was to determine the manner in which auditory stimuli are received at the first relay nucleus (dorsal cochlear nucleus), the modulatory area (midbrain reticular formation), and the association cortex (suprasylvian gyrus). The assumption is that the amplitude of an evoked response indicates a degree of information significance, i.e. a large response contains more information regarding the stimulus than a small response (39).

During the control state, the auditory response is smallest during dream [rapid eye movement (REM)] sleep, larger during the awake state, and largest during

spindle sleep (Figure 5). This correlation between the AER amplitude and configuration and the spontaneous behavioral state is also noted during the anesthetic states (1, 3, 8). The reticular response was absent during all stages of anesthesia. During stages I and II, the AER in the cochleus is equal and the cortical slightly smaller than the awake control. During stage III the AER in the cochleus is initially larger than during stages I and II and is slightly reduced during plane 4. The AER in the cortex was progressively reduced during stage III.

These data led to the conclusion that the reticular formation modulates the auditory signal peripheral to the cochlear nucleus (Figure 6). This would explain the reduced size of the evoked response during stages I and II when reticular activation is marked and modulation is likewise active. During the later phase of

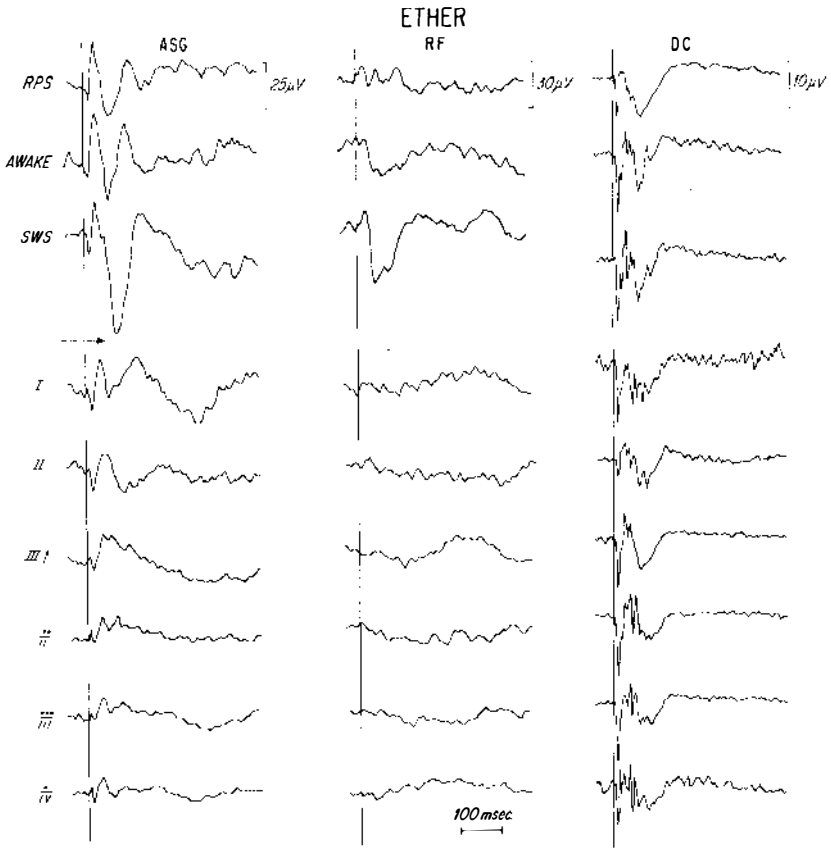

Figure 5 Comparison of the computed averaged auditory evoked response to 40 clicks during control [wakefulness, slow wave sleep, and rhombencephalic phase of sleep (RPS), REM or dream sleep] and ether (10–40%) anesthesia recordings from cat brain: anterior suprasylvian gyrus (ASG), midbrain reticular formation (RF), and dorsal cochlear nucleus (DC) (8).

stage II activity, the animal shows neither electrical nor behavioral arousal, the evoked potentials are slightly larger than controls, and the units appear to fire in synchronous bursts. Since the arousal response disappears concurrently with this intermittent bursting of units, it appears that the reticular unit activity has undergone a partial functional disorganization (40, 41) and while highly excitable, it exerts a reduced control over the level of arousal and sensory modulation (Figure 6). As

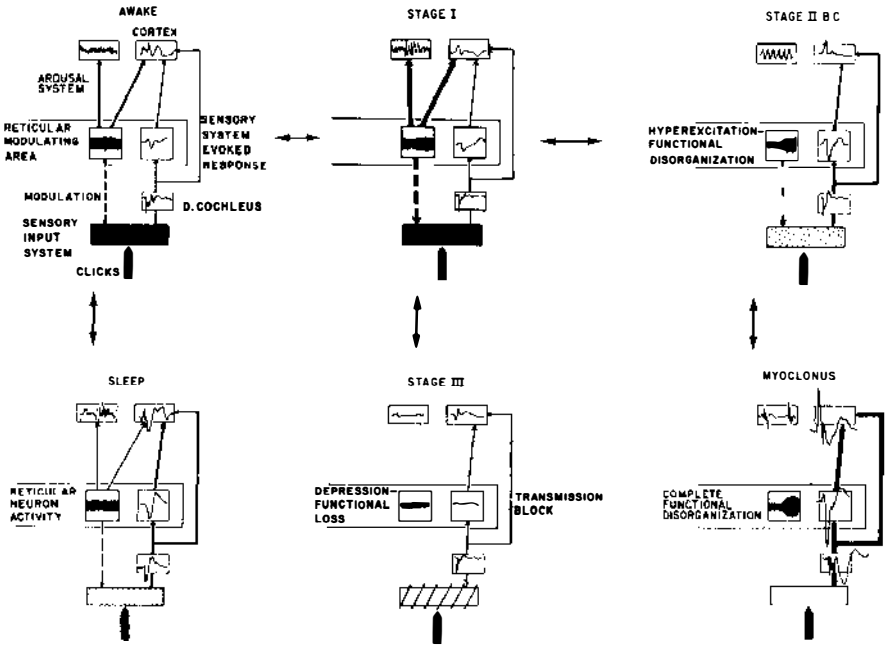

Figure 6 Diagrammatic representation of the control mechanism for sensory input and arousal. Each frame contains the depiction of characteristic evoked potentials at the dorsal cochleus, reticular formation and association cortex, reticular unit activity, and cortical EEG (*upper left box*). The six states shown are awake control to slow wave sleep or stage I, stage I passing to either stage II or stage III, and stage II passing to myoclonus. The sensory input system is depicted by the varying shades indicating degree of filtering as influenced by reticular modulation (*broken lines*). The thickness of the lines denotes qualitative degree of effectiveness; absence of the line denotes complete loss of action.

During control states the reticular unit activity and modulation of sensory input are greatest during wakefulness and least during sleep; therefore the evoked responses are least during wakefulness and greatest during sleep. Stage I results in slightly greater modulation than during wakefulness; thus auditory-evoked responses are slightly smaller. During stage III, reticular unit activity is markedly depressed, there is no sensory modulation, and there is a reduced transmission of sensory signal through CNS. Therefore, the AERs are reduced beyond the cochleus. In contrast, during myoclonus reticular units are hyperexcited but functionally disorganized, there is no sensory modulation and no transmission block; thus the AERs are large throughout the CNS. (Modified from 39.)

this functional disorganization becomes more profound, the EEG pattern changes to the spiking phase, and the bursting pattern of unit activity becomes more pronounced. At this time there is a more profound loss of reticular modulation, the sensory input becomes markedly elevated, and the evoked responses in all brain areas are enlarged (Figures 6, 7).

During stage III, plane i (Figures 5, 6), the reticular unit activity falls rapidly; thus the increase in size of the AER during plane i is indicative of the loss of reticular modulation function along with the loss of the arousal response. The reduction in the amplitude of the AER in the reticular formation and cortex during stages

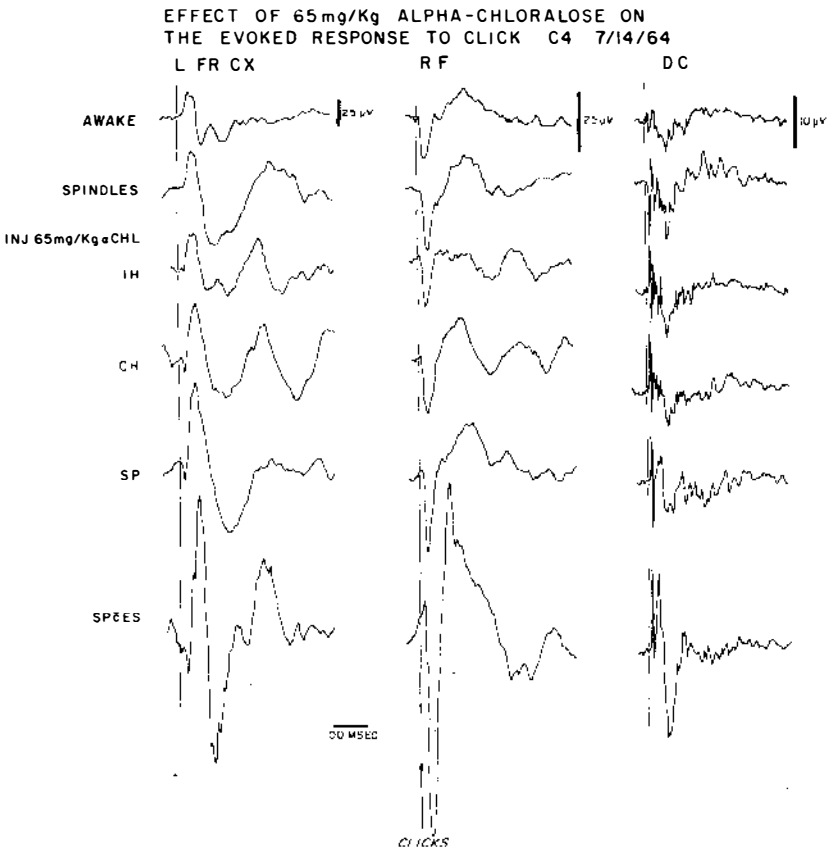

Figure 7 Comparison of the computed average evoked response to 40 clicks in the left frontal cortex (L FR CX), midbrain reticular formation (RF), and dorsal cochlear nucleus (DC) following injection of 65 mg/kg α-chloralose (α-CHL). Stage II-A, intermittent hypersynchrony (IH); stage II-B, continuous hypersynchrony (CH); stage II-C, spikes (SP); myoclonus, spikes with electrical silence (SP with ES) (39).

III–ii–iv while the cochlear response remains large suggests a further direct depressant action of the anesthetic on the transmission of the sensory signal from the cochlear nucleus to the reticular formation and cortex. Alternately this could be due to a direct reduction in responsiveness of the reticular and cortical neurons to the transmitted signal. Schlag & Brand (10) presented evidence that no such depressant action occurs on cortical neurons, since they were unable to demonstrate significant changes in the electrical activity of the isolated cortex prior to deepest anesthesia. The persistent AER in the cochlear nucleus even during deep anesthesia implies that anesthetics during stage III have little direct action on the auditory system peripheral to, and at, the cochlear nucleus. Rather the anesthetics exert a profound inhibition on neuronal transmission, thus preventing the propagation of the auditory response from the cochlear nucleus to the more central areas of the CNS (Figure 6).

DISCUSSION

The elevated reticular formation multiple unit activity during wakefulness and during drug-induced stages I and II is of interest in view of the reports by Rossi & Zirondoli (9) and Schlag & Brand (10) that connections between the midbrain reticular formation and cortex are necessary for the induction of cortical desynchronization during early stages of anesthesia. During stage III anesthesia there is a progressive fall in the level of reticular unit activity. Thus, since two of the four stages of anesthesia manifest properties of CNS excitation the anesthetic state should not be characterized solely as a progressive CNS depression (6). Nitrous oxide is not sufficiently potent to induce depths greater than stage II, and since its actions appear to be solely excitatory it should not be regarded as a CNS depressant. Studies of nitrous oxide action on dogs at greater than 1 atm indicate that anesthesia does occur followed by seizures at the higher atmospheres. Thus, at these higher atmospheres nitrous oxide functions as a cataleptic anesthetic similar to phencyclidine, α-chloralose, or γ-hydroxybutyrate (E. L. Frederickson, personal communication). While diethyl ether induces all four stages of anesthesia, pentobarbital and halothane have less of an initial excitant action than does ether in that they do not induce stage II hallucinatory action following the stage I excitation.

The interpretation of the mode of action of the various anesthetic agents as presented in the continuum of anesthetic stages suggests that the concept of a single anesthetic state is not valid. Because drugs induced both CNS catalepsy or depression (Figure 8), both of which are regarded as states of anesthesia, it seems that it is vital when using these agents that the user be keenly aware of the specific type of agent being used. In addition, a search for a unifying single neurochemical or neurophysiological mechanism to explain the basis of anesthetic action is frivolous. A functional definition of the anesthetic state (5) could be a drug-induced stage that makes the subject relatively unresponsive to painful stimuli and amnestic. This state can be achieved by CNS stimulation or depression (Figure 8). The ultimate neurological basis is the functional control of the reticular activating system. This system can be inhibited (stage III) resulting in functional depression or hyperexcitation (stage II-C) resulting in a functional disorganization, either of which will result in

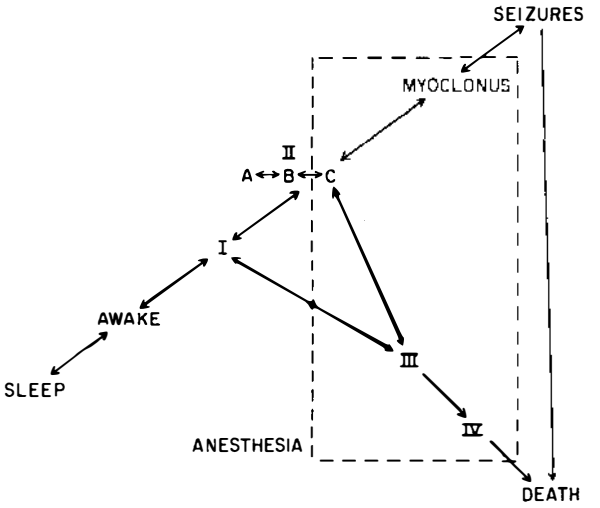

Figure 8 Schema indicating anesthetic states of cataleptic anesthesia (stage II-C and myoclonus) or depressant anesthesia (stage III, IV). Cataleptic representing CNS excitation and depressant representing CNS depression.

a loss of reticular arousal action resulting in unresponsiveness (Figure 6). The amnestic effect of these agents can likewise be presumed to result from a functional disorganization of the CNS networks involved in the process of memory, by either depression or hyperexcitation (28).

SUMMARY

The major concepts presented in this review can be summarized as follows: 1. There is a multidirectional continuum of anesthetic states—some represented by CNS excitation and others by depression. 2. The reticular activating system is influenced by all anesthetics; some inhibit its action (stage III) and some hyperexcite the system resulting in a function disorganization (stage II-C). 3. Some agents traverse both excitation and depression, diethyl ether (I, II, III). 4. Others induce only stage II —catalepsia, e.g. nitrous oxide, ketamine, γ-hydroxybutyrate, α-chloralose, phencyclidine, trichlorethylene, and enflurane. 5. Others induce no stage II but progress directly from stage I to stage III, e.g. halothane and barbiturates. 6. Cataleptic agents may induce further CNS excitation manifested by seizures, e.g. γ-hydroxybutyrate, phencyclidine, ketamine, α-chloralose, trichlorethylene, and enflurane. 7. The functional definition of surgical anesthesia is: a stage induced by a drug that makes the subject relatively unresponsive to painful stimuli and amnestic. Thus, the subject does not respond during surgery and cannot recall what happened afterwards. This state can be achieved by functional disruption of CNS systems by marked stimulation or depression.

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