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THE CATALEPTIC STATE INDUCED BY KETAMINE: A REVIEW OF THE NEUROPHARMACOLOGY OF ANESTHESIA

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Summary—There is a multidirectional continuum of anesthetic states, some represented by CNS excitation and others by depression. The reticular activating system is influenced by all anesthetics, some inhibiting its action (Stage III) and some hyperexciting the system which results in a function disorganization (Stage II C). In both cases the result is a loss of the arousal response. Some agents traverse both excitation and depression, i.e. diethyl ether (Stages I, II, III); others induce Stage II—catalepsia, i.e. trichlorethylene, nitrous oxide, ketamine, γ-hydroxybutyrate, phencyclidine and ethrane; while others induce no Stage II but progress directly from the excitement of Stage I to Stage III, i.e. halothane and barbiturates. Cataleptic agents may induce further CNS excitation manifested by seizures, i.e. γ-hydroxybutyrate, phencyclidine, trichlorethylene, and ethrane.

The functional definition of surgical anesthesia is: A state induced by a drug which makes the patient relatively unresponsive to painful stimuli and amnestic. Thus the patient does not respond during surgery and cannot recall what happened. This can be achieved by CNS stimulation or depression. The anesthetic state induced by ketamine can be described as a cataleptic anesthetic state.

THE DIFFUSE group of agents which induce anesthesia are universally characterized as having the property of inducing CNS depression (GOODMAN and GILMAN, 1956). The progressive depression induced by these agents was fitted to a schema by GUEDEL (1937). He describes the stages of anesthesia as a progressive decrease in CNS excitability: Stage I—excitation, Stage II—delirium, Stage III—surgical anesthesia and Stage IV—medullary paralysis. It should be pointed out that the descriptive terms used to denote the first two stages of anesthesia indicate excitation or increased stimulation rather than CNS depression.

The vertical stratification of the brain proposed by LIVINGSTON, HAUGEN and BROOKHARDT (1954) visualized the CNS as composed of three highly interrelated but vertical systems: the specific sensory, the nonspecific sensory and the motor systems. The nonspecific sensory system was conceived as having the responsibility of 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 of MORUZZI and MAGOUN (1949). Since the reticular formation was demonstrated to be a vital system for the control of wakefulness, several

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investigators attempted to relate both sleep and anesthesia to altered functions of this reticular system. The reticular formation is very sensitive to changes in the spontaneous wake–sleep cycle (WINTERS, MORI, SPOONER and KADO, 1967b) and is likewise sensitive to states induced by various anesthetics (MORI, WINTERS and SPOONER, 1968; WINTERS, MORI, WALLACH and MARCUS, 1969). This statement, "to states induced by various anesthetics", is the crucial point. The question is: Do all agents used in anesthesiology induce the same state? And is the state characterized by CNS depression? if not, then what are the anesthetic states? Without clear-cut answers to these questions it is not possible to discuss the neurophysiology of the anesthetic state induced by ketamine.

There is a bias toward considering subjects asleep or depressed when lying down and immobile, and hyperexcited when moving around. In the hyperexcited cataleptic and preconvulsant states, subjects are likewise immobile, but their CNS is highly activated. The behavioral state of subjects cannot be determined by looking at them, nor can the functional state of the brain be determined by merely observing the subject. The loss of the righting reflex, which is the classical pharmacological test for determining CNS depression, sleeping time or anesthesia time, is completely misleading. This technique only tests for immobility, not functional activity of the CNS. Therefore, to examine the level of excitability of the brain it is necessary to place electrodes in various parts of the brain and examine the brain wave activity during the various states of normal behavior, such as wakefulness and sleep, and during anesthesia. The correlation of the EEG patterns, unit activity, evoked response to stimuli and gross behavior forms the basis for a more meaningful examination of drug-induced states.

Phencyclidine (Sernyl®), the parent compound to ketamine, was introduced as an anesthetic agent in 1957 (GREIFENSTEIN, DEVAULT, YOSHITAKE and GAJEWSKI, 1958). The drug induced an initial amnesia, then analgesia, catalepsy, anesthesia and convulsions (LUBY, COHEN, ROSEBAUM, GOTTLIEB and KELLY, 1959). During emergence, phencyclidine induced a high incidence of acute psychotic reactions and thus was never approved for clinical use. The behavior described, as well as the EEG progression are similar to that of agents which induce the progression of CNS excitation up to generalized seizures described earlier (WINTERS *et al.*, 1969).

An intensive search for analogues which had less propensity for inducing seizures and severe emergence phenomena resulted in the development of ketamine (Ketalar®: Ketaject®). Along with a lesser potency this agent is reported to induce seizures less frequently, to have a shorter duration of action and to cause less severe emergence phenomena (DOMINO, CHODOFF and CORSSEN, 1965). The principle disadvantage of ketamine was reported to be the adverse psychic effects during emergence, such as changes in mood, body image, affect and hallucinations, some of which were sufficiently frightening to the subject that they preferred not to repeat the drug. DOMINO *et al.* (1965) 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 glucose levels. In addition, many of the protective reflexes were maintained during the catalepsia, such as the laryngeal, the pharyngeal, the eyelid and the corneal. EEG studies demonstrated a hypersynchronous slow wave pattern during catalepsia similar to that seen following phencyclidine and other agents which induce a continuum of CNS excitation (WINTERS *et al.*, 1969).

The present study was undertaken to examine the neuropharmacological properties of ketamine on the behavior, EEG and multiple unit activity of unrestrained cats with

chronic cortical and subcortical brain electrodes. In addition, the relationship of ketamine action to wake-sleep cycles was examined. Evidence that ketamine induces a cataleptic anesthetic state will be presented.

METHODS

A total of 21 experiments were performed on 16 adult female cats with chronically implanted cortical and subcortical electrodes. The behavioral criteria for each level of excitability were based on the assessment of the general activity, posture and responsiveness of the animal to auditory or tactile stimulation. Salivation, defecation, pupil size, inappropriate behavior, ataxia, abnormal posture and myoclonic jerking were noted. Inappropriate behavior was characterized by the animal moving its head as if visually tracking in space objects which were not visible to the observer.

Recording techniques were described in detail previously (WINTERS *et al.*, 1967b; WINTERS *et al.*, 1969).

Each experiment was preceded by control examination of the animal during paradoxical sleep (PS), wakefulness, and slow wave sleep, followed by a dose of 15–40 mg/kg i.p. ketamine. Post drug observations were obtained for 2–6 days.

REVIEW OF THE ANESTHETIC STATES

Based on neurophysiological findings outlined previously (WINTERS, MORI, SPOONER and BAUER, 1967a; WINTERS and WALLACH, 1970) a multidirectional schema of the progression of states of CNS excitation and depression was proposed to replace that which was implied in the unidirectional schema of GUEDEL (1937). This schema (Fig. 1) states that

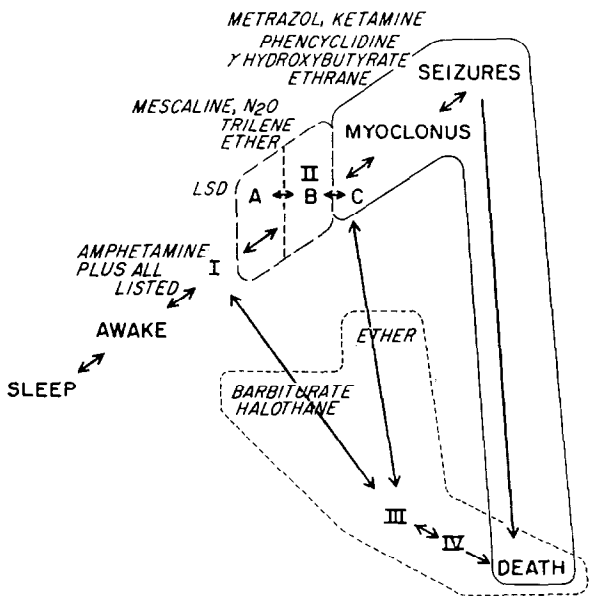

FIG. 1. Schema of reversible progression of states induced by various anesthetic and excitant agents. Stages I, II A, B, C, myoclonus and seizures indicate CNS excitation whereas Stages III, IV indicate CNS depression.

anesthetics and CNS excitants induce an initial excitation (Stage I) characterized by increased motor activity. Some anesthetics then 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 hallucinatory (A, B) then cataleptoid (C) behavior. At this time the subject is likewise 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. The progression is reversible providing the subject does not die either during the convulsions or during Stage IV depression.

There are characteristic patterns of the EEG during the various stages and levels of CNS excitability (Fig. 2). induced by the agents listed in Fig. 1. During Stage I the EEG

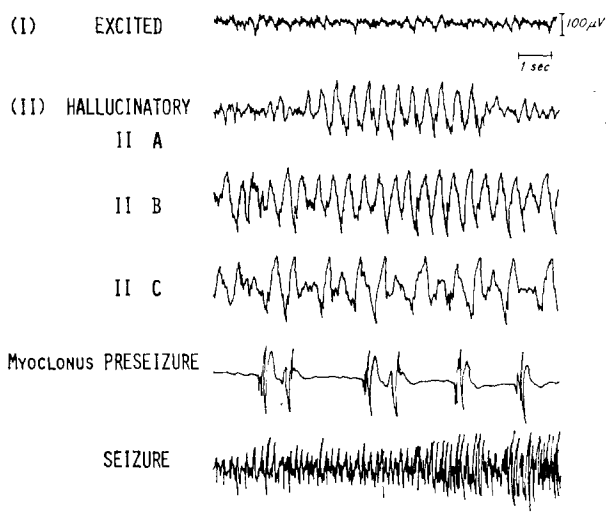

FIG. 2. The progression of CNS excitation with corresponding characteristic EEG patterns induced by the various agents outlined in Fig. 1. Stage I (I), Stage II (II).

is characterized by an activated pattern with high frequency, low voltage activity (desynchronization). During Stage II, the initial phase (A) is characterized by intermittent bursts of high amplitude, 2·5 Hz frequency waves (hypersynchrony) associated with hallucinoid behavior. During II B the hypersynchronous waves are continuous and the bizarre actions of the cats are more intense. During II C the animals lose the righting reflex, maintain abnormal bizarre postures which are cataleptoid and the EEG pattern changes to 1·5 Hz slow waves with occasional spiking. More profound CNS excitation is characterized by myoclonus and the EEG patterns of spike bursts followed by increasingly prolonged periods of relative electrical silence; this phase can continue for prolonged periods of time or culminate in a generalized tonic/clonic seizure with a high frequency, high voltage EEG discharge in all leads lasting up to 1 min in duration. During Stage III there is a progressive reduction in the amplitude of the EEG (Fig. 3) and the general EEG pattern is not as stereotyped as it is for the general group of CNS excitants. Death is characterized by a flat EEG. During emergence each of the preceding EEG patterns reappear but are not as clear-cut as during induction.

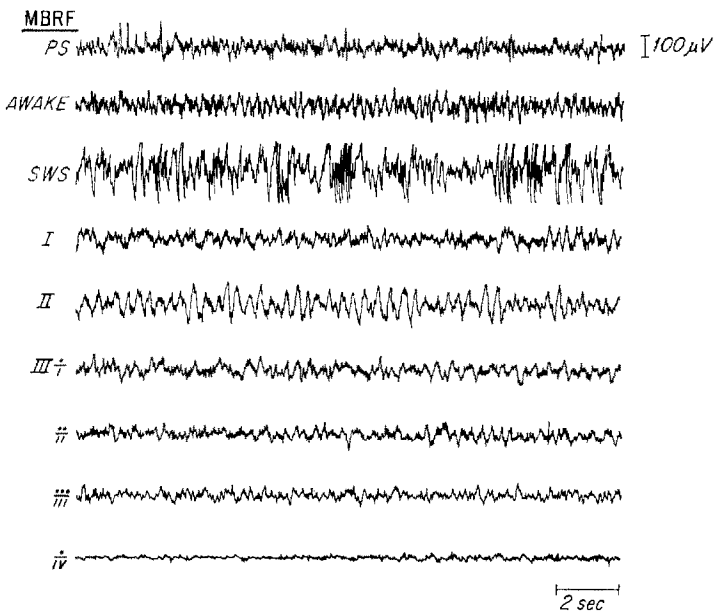

FIG. 3. EEG recorded in the MBRF (midbrain reticular formation) during the control states of PS (paradoxical sleep—dream sleep), awake, and SWS (slow wave sleep) and during Stages I, II and III phases i–iv induced by diethyl ether.

Neuronal activity of the reticular formation during these various phases of excitation correlates with the EEG and behavior (Fig. 4). During Stage I the basal level and fluctuations of reticular unit activity is equal to or slightly elevated over the awake control. During the initial phases of Stage II, i.e. A and B, the level is equal or slightly less than Stage I, but C is clearly lower than Stage I. During myoclonus (spiking) and generalized seizures the width of the unit response, which indicates neuronal excitability, is increased whereas those agents inducing Stage III clearly demonstrate a marked fall in the unit excitability.

A further comparison of the excitability of the CNS during Stage III versus Stage II A and B and myoclonus is demonstrated by the averaged response recorded in the association cortex and the midbrain reticular formation to a series of clicks (Fig. 5). The responses indicate a state dependency during the controls, such that the response is smallest during dream sleep (paradoxical—PS), larger when awake and largest during slow wave (spindle) sleep. Following an anesthetic dose of pentobarbital the response is reduced during Stage III. In contrast, following γ-hydroxybutyrate the response is larger than the awake control during Stage II C and markedly increased during myoclonus.

The progressive electrophysiological changes from Stage I and II up to seizures demonstrates an excitation of the CNS and Stage III and IV demonstrates a depression of the CNS (Fig. 6).

RESULTS

Behavior

Following each dose of ketamine (Fig. 7) there was a rapid appearance of motor excitability and within 2–4 min, ataxia. With the 15 mg/kg dose, the cats then lay in bizarre positions but responded to noxious stimuli, and within 30 min were again ataxic for the next 10 hr.

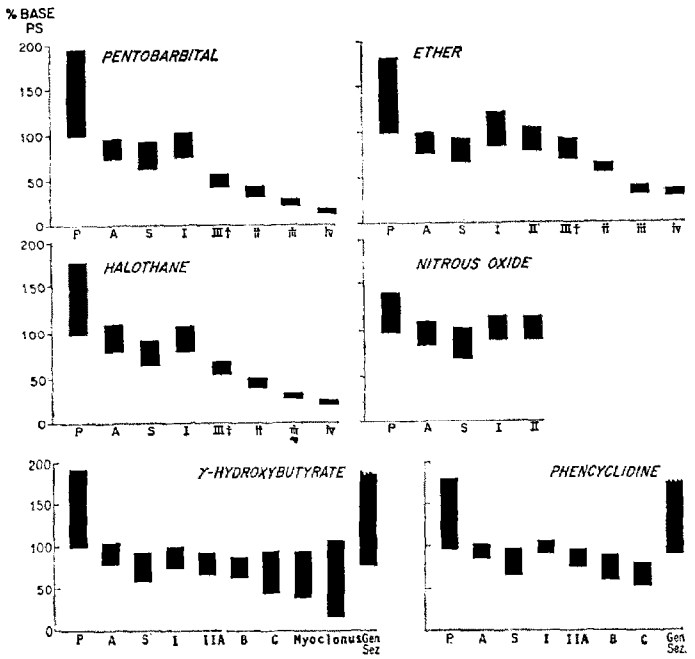

FIG. 4. Bar graphs representing reticular neuronal activity during dream sleep (P), wakefulness (A), and spindle or slow wave sleep (S), and the various stages of CNS excitation (I, II, myoclonus and generalized seizures) and depression (III, i, ii, iii and iv). The height of the bar indicates neuronal excitability. (For details see method section WINTERS *et al.*, 1967b.) (Modified from MORI *et al.*, 1968.)

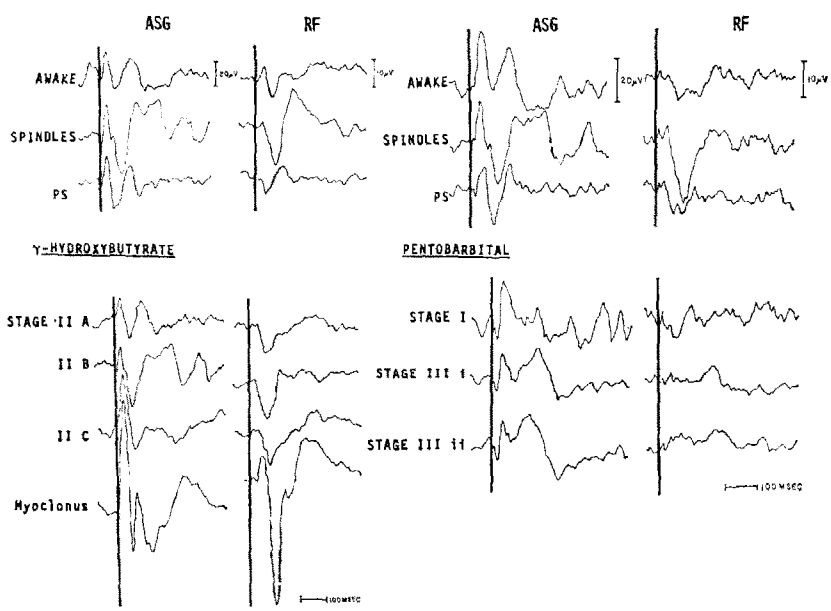

FIG. 5. Comparison of auditory evoked response during control states of awake, dream sleep (PS) and spindle sleep, and following 600 mg/kg i.p. γ-hydroxybutyrate or 40 mg/kg pento barbital. ASG, anterior suprasylvian gyrus; RF, midbrain reticular formation.

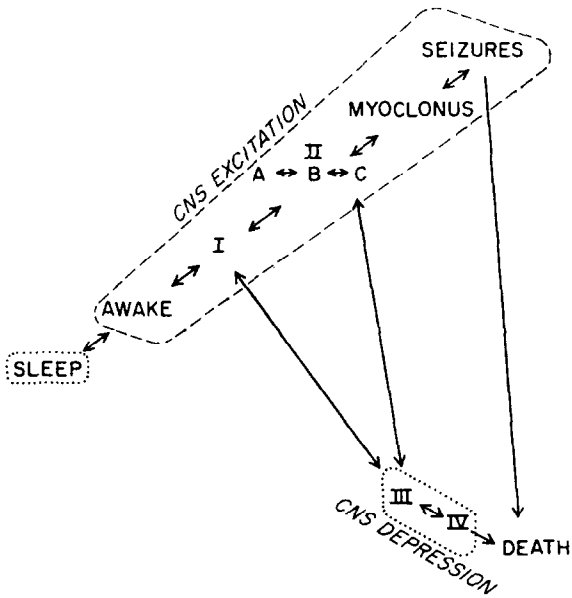

FIG. 6. Multidirectional schema of CNS excitation and depression.

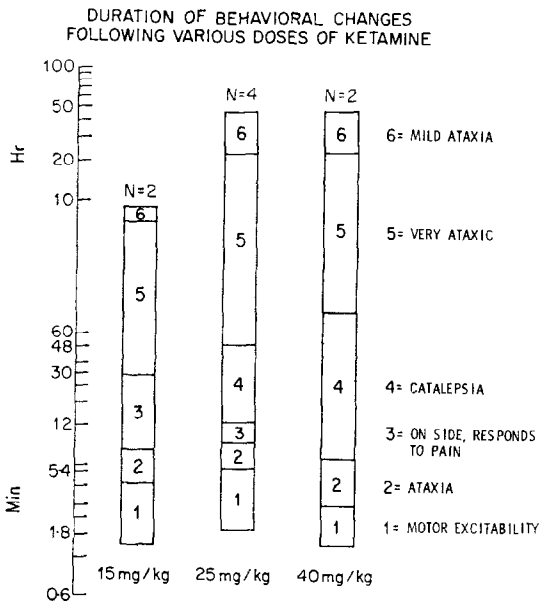

FIG. 7. Duration of behavioral changes following various doses of ketamine.

The moderate dose (25 mg/kg) induced a 45-min period of catalepsy with no response to noxious stimuli followed by ataxia and a return to relative control states in 50 hr. The highest dose (40 mg/kg) induced a 1-hr period of catalepsia followed by ataxia and a return to control after 50 hr. Thus the 15 mg/kg dose did not induce a state of unresponsiveness, whereas the 25 and 40 mg/kg doses did.

EEG

The EEG patterns were related to the above noted behavioral changes (Figs. 8–10). During motor excitation, the pattern was characteristic of an alert EEG with low voltage fast waves (desynchronized); during ataxia with bizarre postures, there was intermittent then continuous 2·5 Hz, high amplitude waves (hypersynchrony); during catalepsia the pattern was continuous 1–5 Hz hypersynchrony with spikes. The time course for these patterns are noted in Fig. 11. Of interest was the appearance of a seizure discharge during catalepsy noted in the dorsal hippocampus following the cataleptic-inducing 25 and 40 mg/kg doses of ketamine (Figs. 9, 10). In both cases the discharge did not spread to adjoining areas and no gross behavioral manifestations of epilepsy could be noted.

Reticular multiple unit activity

The basal height and fluctuation of reticular unit activity remained elevated (Fig. 12) as was noted with the other cataleptic-inducing agents (see also Fig. 4), rather than falling below 40% PS with a marked reduction in fluctuation (excitability) as noted during CNS depression (Fig. 4) (MORI, WINTERS and SPOONER, 1968).

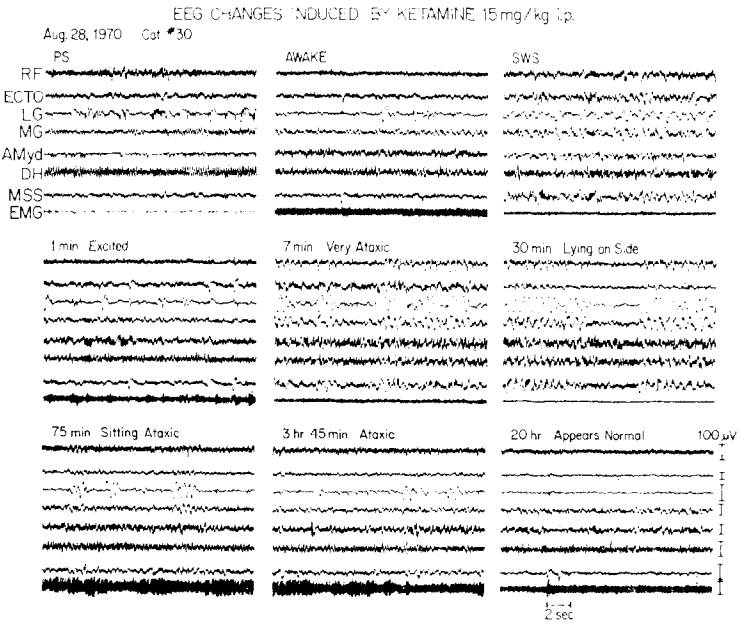

FIG. 8. EEG progression during the control states of dream sleep (PS), awake and slow wave sleep (SWS), and following ketamine 15 mg/kg i.p. RF, midbrain reticular formation; ECTO, ectosylvian gyrus; LG, lateral geniculate nucleus; MG, medial geniculate; AMyd, amygdala; DH, dorsal hippocampus; MSS, medial suprasylvian gyrus; and EMG, electromyograph.

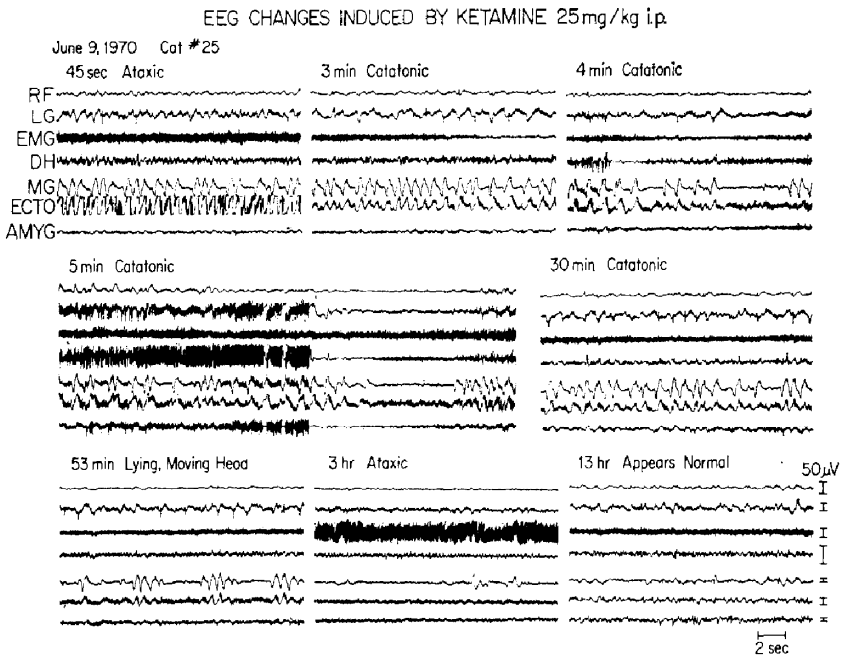

FIG. 9. EEG progression following ketamine 25 mg/kg i.p. (see Fig. 8).

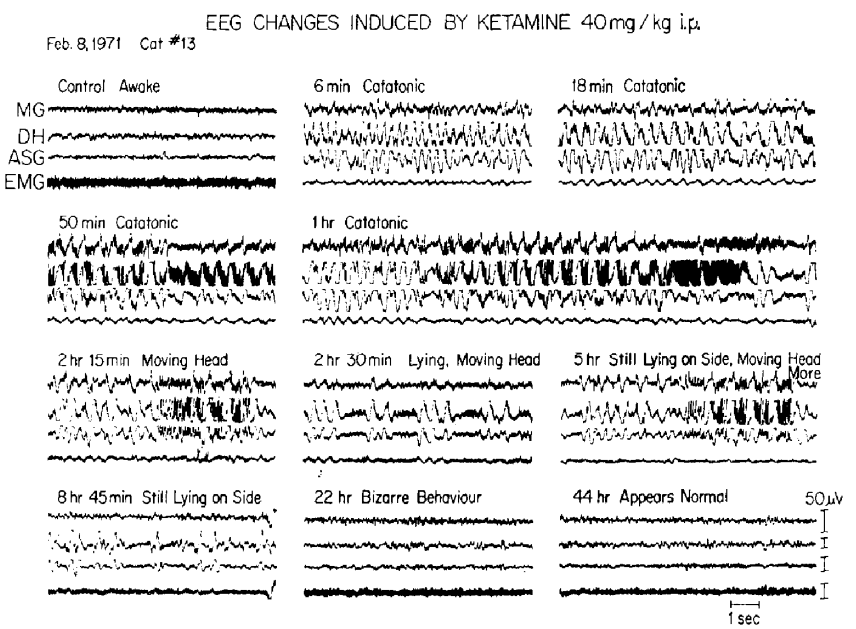

FIG. 10. EEG progression following ketamine 40 mg/kg i.p. (see Fig. 8).

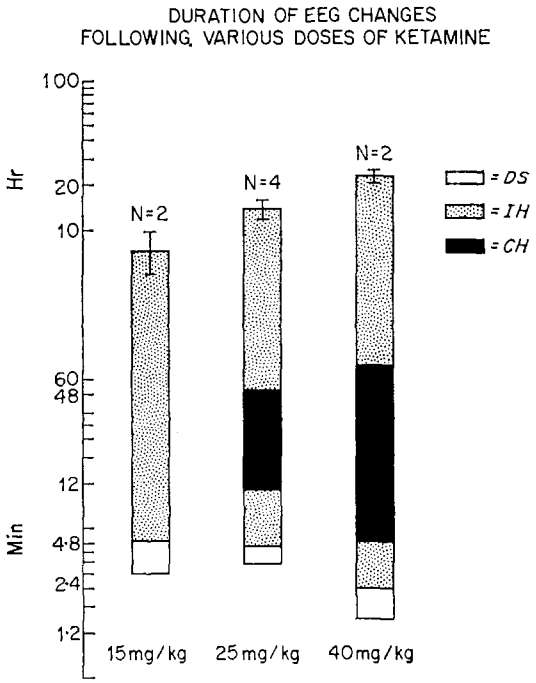

FIG. 11. Duration of EEG changes following various doses of ketamine. Stage I, desynchronized (DS); Stage II A, intermittent hypersynchrony (IH); Stage II B, C, continuous hypersynchrony (CH).

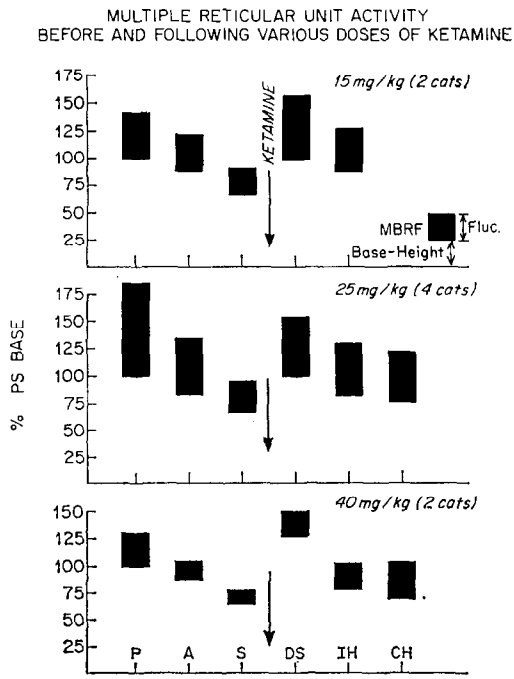

FIG. 12. Bar graphs representing reticular neuronal activity during the control states of paradoxical sleep (P), awake (A), and slow wave sleep (S) and following 15, 25 and 40 mg/kg ketamine i.p.; Stage I (DS), Stage II A (IH), and Stage II B, C (CH). MBRF, midbrain reticular formation. (See Fig. 4 and WINTERS *et al.*, 1967b.)

The behavioral, EEG and reticular unit data clearly indicates that ketamine induces actions similar to other CNS excitatory agents (Fig. 1) such as phencyclidine, LSD, mescaline, γ-hydroxybutyrate and pentylenetetrazol (WINTERS *et al.*, 1969) and does not induce a depression of the CNS.

Wake-sleep cycles

Observations of the daily wake-sleep cycles of these cats were examined prior to and following ketamine (Fig. 13). There was almost no dream sleep (PS or REM) during the

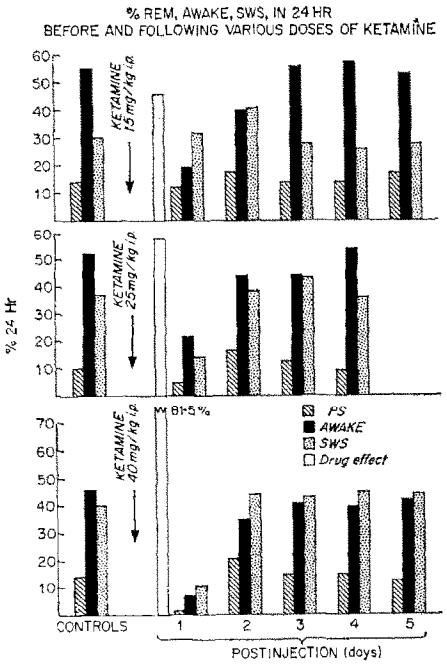

FIG. 13. Averaged per cent dream sleep (PS), awake and slow wave sleep (SWS) for 24-hr periods prior to and post injection of 15 (N=2), 25 (N=4) and 40 (N=2) mg/kg ketamine i.p.

first day following injection of 40 mg/kg ketamine. The 40 mg/kg dose of ketamine induced about 1 hr of catalepsy followed by 18 hr of Stage II A—hallucinatory activity—during emergence (see Fig. 11) and no dream sleep until 23 hr post drug. From this data it is concluded that the so-called emergence dreaming is actually emergence hallucinations (Stage II) and dream sleep is in fact depressed or absent during emergence.

DISCUSSION

The schema of CNS excitation and depression suggests a progression of changes to different levels of excitability or depression, some anesthetics sharing initial properties with drugs of opposite action (Fig. 1). For example, both ether and phencyclidine induce Stage II but ether goes on to induce Stage III and phencyclidine induces generalized seizures. It appears that a hallucinatory state (II A, B) can precede the generalized convulsant state, can precede the CNS depression (III) or can precede the cataleptic anesthetic state (II C).

Any agent which induces a loss of responsiveness and amnesia can be considered an anesthetic (WINTERS *et al.*, 1967a); therefore Stages II C and III both satisfy these criteria (Fig. 14).

The term "dissociative anesthesia" proposed by MIYOSAKA and DOMINO (1968), which implies that the thalamo-neocortex had slow waves but the hippocampus was relatively normal during ketamine anesthesia, does not seem valid since during the cataleptic state induced by 25 and 40 mg/kg ketamine, seizure activity does occur in the hippocampus.

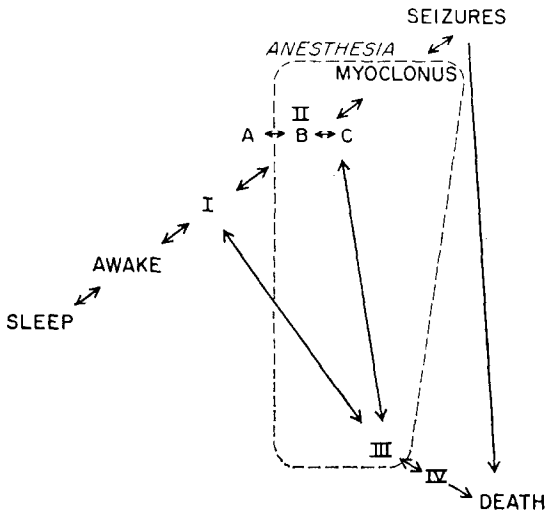

FIG. 14. Schema indicating anesthetic states.

Since the surgical procedures (anesthesia) are performed during the cataleptic state, this is the state during which this type of correlative observation should be made, not at the lower stages of CNS excitation. MIYOSAKA and DOMINO (1968) made their observation in cats receiving 16 mg/kg i.p. ketamine or less, a dose which does not induce Stage II C cataleptic anesthesia. Therefore, the apparent dissociation which they describe was not during the anesthetic state of drug action. A more appropriate term to describe the ketamine-induced anesthetic state would be the term "cataleptic-anesthetic state".

The appearance of hippocampal seizures during the cataleptic state is of great significance. A similar discharge was noted by BRECHNER and FERRER (unpublished findings at UCLA Medical Center) in 2 epileptic human subjects with depth electrodes in the hippocampus for diagnostic procedures. These subjects likewise had no gross manifestations of seizure activity during the limbic seizures induced by ketamine. The induction of epileptiform EEG patterns plus temporal lobe seizures must be kept in mind when using this agent for diagnostic neurological procedures. Subjects with temporal lobe pathology may be triggered into profound seizures with agents such as ketamine and one must be prepared for this occurrence, especially in neurological patients. In addition, the misdiagnosis of iatrogenic epilepsy in a patient receiving ketamine would be tragic.

There is a dream sleep suppression during the 23 hr post drug and an associated 18 hr of Stage II following the cataleptic-anesthetic state induced by 40 mg/kg ketamine. This strongly implies that the so-called emergence dreaming is actually the emergence delirium of Stage II. Unlike dream sleep, this hallucinatory phase of recovery can be manifested by bizarre behavior which should be followed carefully.

A final point regarding ketamine involves the nature of its CNS action. The Stage II hallucinatory action of ketamine is not unlike phencyclidine (which is known on the streets as PCP, Peace, Angel's Dust, or Hog), nitrous oxide, diethyl ether, mescaline or LSD-25 (Fig. 1). Each of these agents has a history of abuse when used for hallucinogenic inducing purposes (WINTERS *et al.*, 1969; KEYS, 1963). There are now a few reports of ketamine street use (REIER, 1971). With the increased medical and veterinary use of ketamine it will undoubtedly become a more popular street drug. It is vital that those who use this agent be aware of this potential hazard both from the medico-legal standpoint as well as for the protection and safety of the patient. We are now at the point where a careful evaluation of abuse liability must be considered when deciding the efficacy of drugs for clinical use.

The interpretation of the mode of action of anesthetic agents as presented in this schema suggests that the concept of a single anesthetic state is not valid. Since both CNS excitant and depressant drugs can induce a state of anesthesia (Fig. 14), it seems vital that those utilizing these agents be keenly aware of the specific type of anesthetic agent being used (Fig. 1). Ketamine should be classified as an excitatory agent capable of inducing a cateleptic anesthetic state.

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