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RETICULAR MULTIPLE UNIT ACTIVITY DURING A PROGRESSION OF STATES INDUCED BY CNS EXCITANTS. III[1]

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Prior studies utilizing EEG, gross behavior and auditory evoked response techniques have demonstrated that some agents although reported to be "anesthetics" should be, in fact, classified as "epileptogenics" (Winters and Spooner 1965a, b; Winters *et al.* 1967a). In order to assess more critically the neuronal state induced by these agents, *e.g.*, phencyclidine and gamma-hydroxybutyrate, it is necessary to utilize methods which are more sensitive to changes in neuronal activity than those afforded by techniques such as the gross EEG and behavioral responsiveness (Winters and Spooner 1965a, b; Winters *et al.* 1967a), loss of the righting reflex (Marcus *et al.* 1967), and the size of the evoked response (Mori *et al.* 1968). Continuous monitoring of the activity of neuronal elements in the midbrain reticular formation which is very sensitive to changes in behavioral states (Moruzzi and Magoun 1949; French *et al.* 1953) has been useful in examining neuronal changes during wakefulness and sleep (Winters *et al.* 1967b) and during the various stages of anesthesia (Mori *et al.* 1968). The technique of monitoring the unit activity of a large population of neuronal elements described previously (Arduini and Pinneo 1962; Schlag and Balvin 1963; Buchwald *et al.* 1965; Winters *et al.* 1967b) seems particularly useful for the present study since drug-induced epileptoid states are phenomena which probably arise from changes in neuronal aggregates.

In the present study we will attempt to compare the action of six compounds which induce varying degrees of CNS excitation: amphetamine, lysergic acid diethylamide, mescaline, phencyclidine, pentylenetetrazol and gamma-hydroxybutyrate. The changes in reticular multiple unit activity (RUA) will be compared with the changes in gross behavior and EEG in an attempt to clarify some of the underlying processes involved in these induced states, and a continuum of excitatory states and two types of generalized seizures will be discussed.

METHODS

A total of 70 experiments was performed on ten adult cats of both sexes with chronically implanted cortical and subcortical electrodes. Prior studies described in detail the techniques utilized in the acquisition of the EEG, gross behavior (Winters 1964), and multiple unit activity (Winters *et al.* 1967b).

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, abnormal posture, myoclonic jerking, and generalized clonic and/or tonic seizure ac-

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tivity 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.

EEG patterns induced by the drugs in the present study have been reported previously: *d*-amphetamine 2–8 mg/kg or methamphetamine 2 mg/kg (Bradley and Elkes 1957); lysergic acid diethylamide (LSD-25) 50–100 μg/kg (Heath and Mickle 1960; Adey *et al.* 1962); mescaline 20–30 mg/kg (Bradley and Elkes 1957); phencyclidine 2–8 mg/kg (Winters *et al.* 1967a); gamma-hydroxybutyrate 200–800 mg/kg (Winters and Spooner 1965a,b, 1966); and pentylenetetrazol 20–25 mg/kg (Ajmone Marsan and Ralston 1957; Okuma 1960).

Each agent induced similar results in a minimum of four different cats before a characteristic pattern of events was accepted; while each cat did not receive all of the drugs studied, all cats received gamma-hydroxybutyrate for comparison. No animal received drug more often than once every 10 days. Each agent was administered intraperitoneally in sufficient dosage to obtain the desired action rather than in pre-set doses. It was not the intent in this study to evaluate the potency or rate of action of each agent, but rather to examine the progression of induced states.

Saline, drug carrier, or ineffective doses of each drug were administered for control observation, and the slight activation of the EEG, RUA and behavior due to handling of the animal and/or peritoneal irritation disappeared within 5 min in all experiments. When the initial excitation exceeded 10 min, it was assumed that the excitation resulted from central activation rather than peritoneal irritation, since similar activation of the EEG accompanied by elevation of RUA was demonstrated in ten gallamine triethiodide (Flaxedil®) immobilized cats following either gamma-hydroxybutyrate (5 experiments) or pentylenetetrazol (5 experiments) given intravenously (unpublished). An animal with a jugular vein implant inserted chronically likewise demonstrated an initial period of excitation after gamma-hydroxybutyrate administration. In the acute studies (unpublished), the blood pressure rose minimally prior to the onset of generalized seizures; thus the initial excitation does not appear to be related to pressure changes.

Recordings of the multiple unit activities were obtained from the same gross electrode which was simultaneously recording the EEG in the midbrain reticular formation. The stereotaxic placement of the electrodes was either at A 3, L 3, H −1 or A 4, L 2, H −1 (Jasper and Ajmone Marsan 1953) and was verified histologically in six cats. The electrical activity obtained from each bipolar electrode (diameter 160 μ) was AC coupled into the first stage of the EEG machine (Grass Model 6). The high frequency components of the electrical signals were tapped off at the second amplifier stage (terminals J-3 and J-4) through a 100 pF capacitor; thus electrical activity above 500 c/sec was shunted through the capacitor. The electrical activity below 500 c/sec continued from the 1st stage amplifier to the final EEG amplifier stage with suitable filtering and amplification, and this standard EEG signal was expressed on the paper write-out of the EEG machine. Meanwhile the high frequency component, after passing through the 100 pF capacitor, was amplified and the component above 2500 c/sec shunted to ground by passing the signal through a Tektronix 122 preamplifier (set at 1 kc), resulting in a bandpass system centered at 1000 c/sec with −3 dB points at 500 c/sec and 2500 c/sec. This activity representing multiple unit activity was displayed on a Tektronix 502 oscilloscope. To obtain a continuous recording of the change in unit activity before and after drug administration, the filtered signals were passed through the cathode follower output of the oscilloscope, rectified, smoothed, and recorded continuously on a slow-moving strip chart recorder (Brush 280). Thus, the data were obtained as both a large population of raw units observed on the oscilloscope and the amplitude demodulated signal recorded on the strip chart recorder (Winters *et al.* 1967b). At the completion of each experiment the system noise was tested utilizing a dummy plug containing a 10 kΩ resistor across the input in place of the animal (see Winters *et al.* 1967b for a discussion of relationship of this signal to unit activity). The change in both the basal level of unit activity and the fluctuation of activity from this basal level was examined, since the basal level of the unit activity is directly related to the width of the envelope of raw units; when the envelope is

wider the DC value of the basal level is higher and, conversely, when the envelope is smaller the basal level falls to a level closer to DC 0. As discussed previously (Winters *et al.* 1967b), the change in the envelope width suggests that the appearance of larger spikes indicates that a larger number of units are firing simultaneously, and the greater the number and frequency of units firing the greater the chance of summation of units due to coincident unit firing. The fluctuation in unit activity indicates that the firing pattern of the population of units alternates above the basal rate, and the height of these bursts of unit activity is a reflection of this pattern expressed as the fluctuation of unit activity.

Each experiment was preceded by control examination of the animal during rhombencephalic (paradoxical) sleep, wakefulness, and slow wave sleep. Following the establishment of control levels for these three states (Winters *et al.* 1967b), the drug was administered and the changes in the basal level and fluctuation of multiple unit activity were observed.

RESULTS

All of the agents studied induce a similar general pattern of EEG and behavioral change and differ mainly in the degree of progression (Fig. 1). The changes in the basal level and fluctuation of unit activity induced by each agent correlate with the changes in gross behavior and EEG. The progression of changes induced by each drug can be delineated according to the EEG patterns as follows.

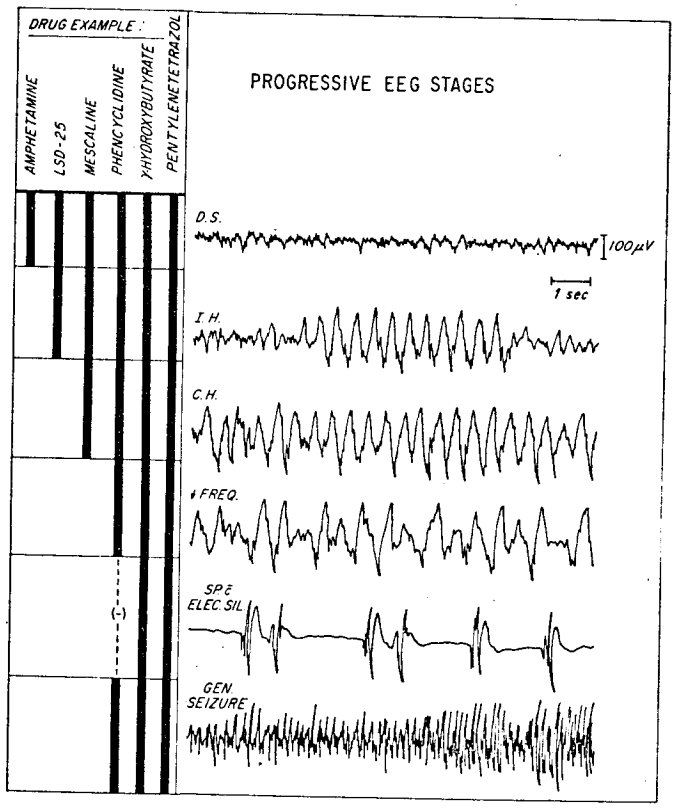

Fig. 1

A representation of the states and EEG stages induced by various drugs, as follows: desynchronization (D.S.); intermittent 2.5–3 c/sec hypersynchrony (I.H.); continuous 2.5–3 c/sec hypersynchrony (C.H.); reduced frequency (1.5 c/sec) hypersynchrony (↓ Freq.); spikes with electrical silence (Sp. & Elec. Sil.); and generalized seizure (Gen. Seizure). The vertical bar under each drug represents the progressive state(s) which were induced by each agent in the present study. Spikes with electrical silence were rarely noted following phencyclidine. In general, the EEG patterns were similar and each agent differed mainly in the rate of progression and the total progression induced.

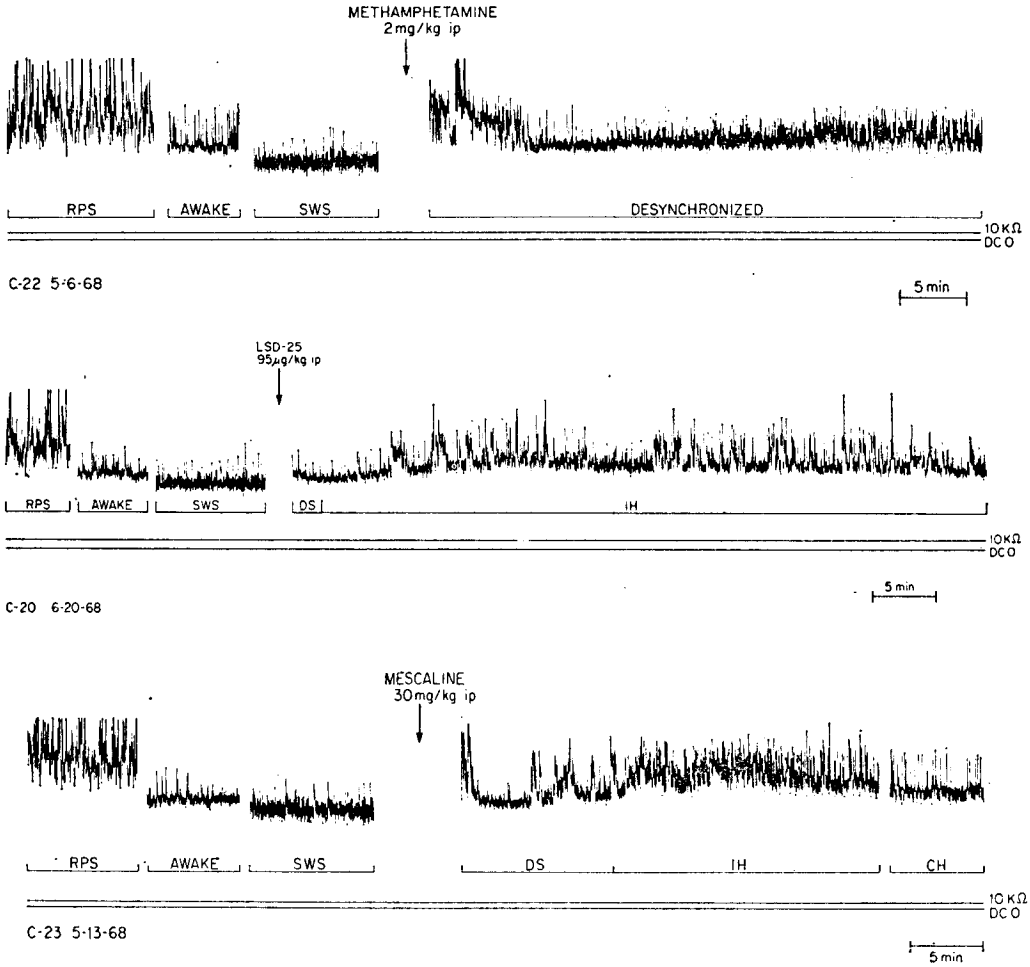

Fig. 2

Comparison of the amplitude demodulated signals of the midbrain reticular formation unit activity during the control states of RPS (rhombencephalic phase of sleep), Awake, and SWS (slow wave sleep) and following administration of methamphetamine, LSD-25 and mescaline. The lowest line (DC 0) represents the system balanced to zero; the 10 kΩ line represents the system noise level with a 10 kΩ resistor across the input. Changes in basal unit activity are measured as the distance from the base of the unit activity tracing to the 10 kΩ line. The fluctuation is the width of the excursion from the basal reticular unit activity level to the peaks. See legend to Fig. 1.

A. *Desynchronized*

Amphetamine, LSD-25, mescaline, phencyclidine, gamma-hydroxybutyrate, and pentylenetetrazol all induced EEG desynchronization, behavioral hyperactivity plus a slightly increased basal level of RUA above awake control levels and no significant change in fluctuation (Fig. 2 and 3).

B. *Intermittent hypersynchrony*

All of the agents examined except amphetamine induced EEG patterns of intermittent 2.5–3.5 c/sec hypersynchrony, inappropriate behavior, hyperactivity, pupillary dilation, salivation, occasional defecation and a slight increase in the level of RUA above the desynchronized state (Fig. 2 and 3). Pentylenetetrazol traverses this phase so rapidly that this phase is often not seen.

C. *Continuous hypersynchrony*

LSD-25 effects did not progress to this state.

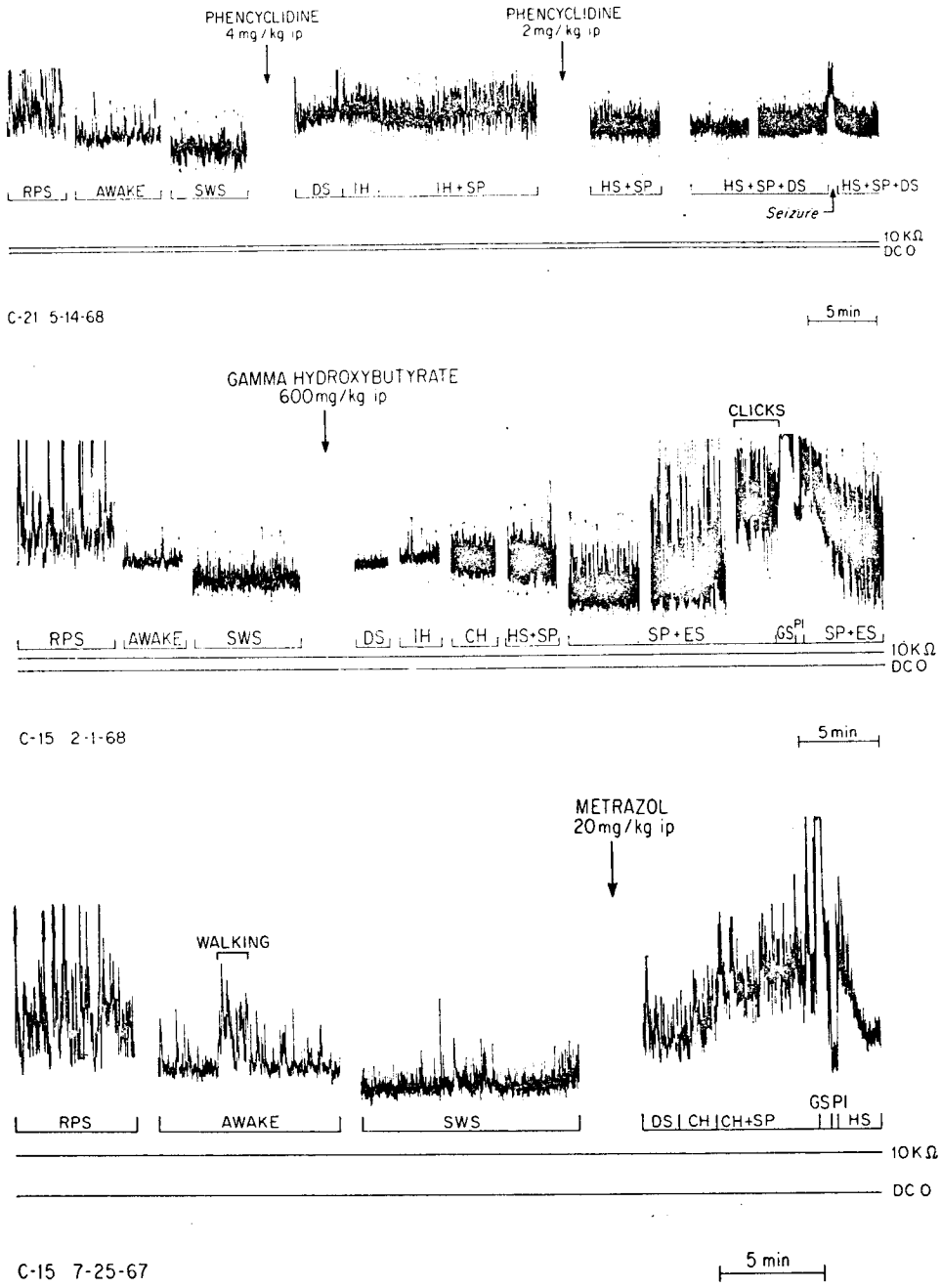

Fig. 3

Comparison of the amplitude demodulated signals of the midbrain reticular formation unit activity during control states and following phencyclidine, gamma-hydroxybutyrate and pentylenetetrazol (Metrazol). Intermittent hypersynchrony and spiking (IH + SP); hypersynchrony and spiking (HS + SP); hypersynchrony, spiking and desynchrony (HS + SP + DS); spiking and electrical silence (SP + ES); generalized seizure (GS); post-ictal depression (PI). See legends to Fig. 1 and 2.

Mescaline, phencyclidine, gamma-hydroxybutyrate and pentylenetetrazol all induced rigid postures with fixed gaze, pupillary dilation, reduced responsiveness to stimuli, inappropriate behavior and continuous 2.5–3 c/sec hypersynchronous EEG waves.

There were two types of RUA during this phase. Mescaline and pentylenetetrazol induced no change, or a slight elevation in basal unit level and no changes in the fluctuation compared to intermittent hypersynchrony; phencyclidine induced the same level as or slightly lower than intermittent hypersynchrony and reduced fluctuation, whereas gamma-hydroxybutyrate induced a decrease of the basal RUA level below the awake control level with an increased fluctuation (Fig. 2 and 3).

D. *Reduced frequency hypersynchrony with spikes*

This state was not achieved with mescaline. Gamma-hydroxybutyrate induced a state wherein the animal lay on its side with the head and limbs in abnormal positions and exhibited a fixed gaze, pupillary dilation, and unresponsiveness to stimuli; the EEG pattern was characterized by 1.5 c/sec slow waves and spikes and there was a

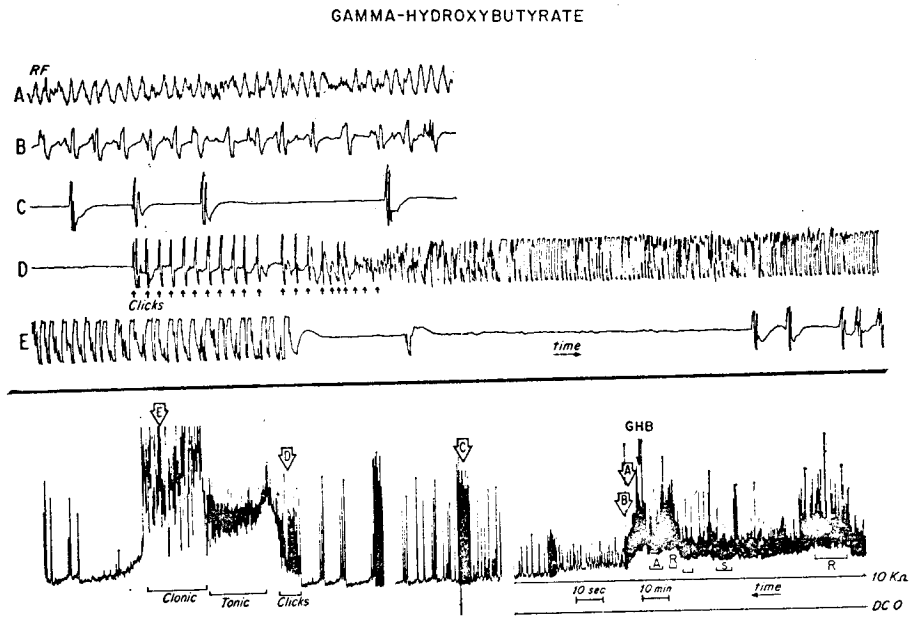

Fig. 4

Comparison of various stages (*A–E*) of gamma-hydroxybutyrate (GHB) induced EEG changes with the corresponding amplitude demodulated multiple unit activity recording (*A–E* in arrows) from the same electrode implanted in the midbrain reticular formation.

EEG (*upper portion*): 2.5 c/sec hypersynchrony (*A*), 1.5 c/sec hypersynchrony (*B*), spontaneous spikes bursts with varying periods of electrical silence (*C*), induction of generalized seizure bursts by presentation of clicks during *C* (*D*), termination of generalized seizure from *D* followed by post-ictal depression and a return to pattern noted in *C* (*E*).

Multiple unit activity (*lower portion*): Control unit activity during rhombencephalic sleep (R), slow wave sleep (S), and wakefulness (A) and following 800 mg kg GHB. Arrows with letter inserts denote corresponding EEG patterns. Time runs from right to left. From start to *B* chart ran at slow speed: 7 mm = 10 min; then the chart speed was periodically increased to 7 mm = 10 sec to demonstrate the intermittent unit bursts. The 2 burst episodes prior to the onset of clicks and the entire seizure progression *D* and *E* were run at the faster chart speed. Note the large amplitude of summated spikes intermittently occurring on a markedly reduced basal firing level starting at *B* and most pronounced between *C* and *D*. The signal to noise ratio (computed by measuring the basal height above DC 0 *vs.* the height above DC 0 of a 10 kΩ dummy load at the input) in this animal was not as good as those noted in the cats shown in Fig. 2 and 3; however, the findings are representative.

fall in the basal RUA level below control slow wave sleep with an increased fluctuation (Fig. 3). Phencyclidine induced 1.5 c/sec slow waves with spiking and periods of desynchronization between slow wave bursts; the animal was rigid and immobile with a fixed gaze and abnormal postures; there was no change in the basal unit level and a reduction in the fluctuation (Fig. 3). Pentylenetetrazol induced behavioral immobility with fixed gaze and rigid abnormal posture, the EEG waves were 1.5 c/sec slow waves with spiking, and the basal RUA level increased above control rhombencephalic sleep level (Fig. 3).

E. *Spikes with electrical silence*

Gamma-hydroxybutyrate induced a period of polyphasic spike bursts separated by increasing intervals of electrical silence lasting up to 1–3 sec, associated with myoclonic jerks, fixed gaze, rigid abnormal posture and a marked fall in the basal RUA level with bursts of markedly increased fluctuations which occurred simultaneously with the appearance of EEG spike bursts (Fig. 3 and 4). Phencyclidine induced an increase in spiking and a slight increase in fluctuation but no change in basal level (Fig. 3). Pentylenetetrazol induced increased spiking, increased rigidity and a rise in the level of unit activity and fluctuation (Fig. 3).

F. *Generalized seizures*

Gamma-hydroxybutyrate, phencyclidine and pentylenetetrazol induced tonic-clonic generalized seizures with a high frequency, high amplitude EEG pattern. The seizure following either phencyclidine or pentylenetetrazol occurred without external stimulation. Following gamma-hydroxybutyrate, the seizure was induced by repetitive auditory, visual or tactile stimulation. The basal level of reticular unit activity was at or above the control rhombencephalic phase of sleep level following phencyclidine, gamma-hydroxybutyrate and pentylenetetrazol, and the fluctuation increased above the level noted during rhombencephalic sleep (Fig. 3 and 4).

G. *Post-ictal depression*

A brief post-ictal depression was noted with gamma-hydroxybutyrate or pentylenetetrazol, followed by a return to the activity noted just before the generalized seizure. During the post-ictal depression the basal level dropped markedly from the level noted during the seizure but did not fall below control levels (Fig. 3 and 4). The phencyclidine-induced seizure was not followed by a post-ictal period, but the pattern noted prior to the seizure reappeared (Fig. 3).

DISCUSSION

The progression of events induced by the agents in the present study implies that three basic states are induced; *i.e.*, an initial excitation, followed by a state characterized by abnormal posture and behavior, and finally, generalized seizures (Fig. 5). During the initial excitation the reticular unit activity changes in a manner similar to the initial excitatory stages (I and II) induced by general anesthetics (see Fig. 5 and Winters *et al.* 1967b; Mori *et al.* 1968).

While the initial state induced in the present study is clearly a behavioral and electrical excitatory state, the second induced state is less clearly understood. This state is characterized by inappropriate behavior coupled with abnormal postures indicative of "hallucinatory" behavior. Obviously one cannot be certain that this induced state in cats is the same hallucinatory phenome-

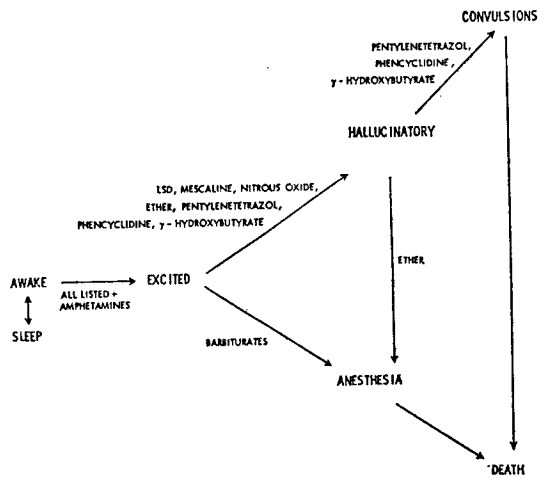

Fig. 5

A proposed schema of states induced by some CNS excitant and depressant agents. The data are compiled from data in the present study and a previous study (Mori *et al.* 1968). See discussion for details.

nor that occurs in man; however, this behavior is pronounced in the cat following agents such as LSD-25, mescaline and psilocybin which induce profound hallucinatory actions in man. In addition to the induction of hallucinatory behavior in man, these agents induce 2.5–3 c/sec hypersynchronous EEG wave patterns during the hallucinatory state which appear to be similar to the hypersynchronous activity noted in cats with these agents (Heath and Mickle 1960). Further, Adey *et al.* (1962) demonstrated that LSD-25 induced an apparent intermittent loss of contact with the environment at the same time that the hypersynchronous 3 c/sec EEG waves appear in the EEG of the cats performing in a T maze. Thus there is strong presumptive evidence that the induced state of intermittent hypersynchrony, inappropriate behavior, and inappropriate postures are, in fact, evidence of a hallucinatory state. The hallucinoid activity preceding the generalized seizure activity induced by these convulsant agents may represent the aura noted clinically prior to a grand mal seizure.

With phencyclidine and pentylenetetrazol, the pre-seizure phase of CNS excitation is associated with a progressive rise in the level of reticular unit activity indicating a progressive rise in the frequency of reticular formation unit firing. However, during the pre-convulsant state induced by gamma-hydroxybutyrate, the basal level of reticular unit activity progressively falls while the intermittent fluctuation of unit activity is markedly increased; thus the units fire less frequently, but when they do fire, they do so synchronously both spontaneously and in response to stimuli (Fig. 4). In contrast, during Stage III anesthesia, the basal level of unit activity is likewise low but the fluctuation is markedly reduced, the units do not fire in bursts and are relatively unresponsive to stimuli (Mori *et al.* 1968). It appears that gamma-hydroxybutyrate induces episodes of refractoriness followed by periods of synchronous responsiveness to stimuli, whereas during general anesthesia the reticular units are continuously unresponsive, presumably due to a profound inhibition.

The amazing similarity of actions induced by the structurally different groups of agents listed in Fig. 5 may indicate that the system affected by these agents involved interference at one of a number of different levels of energy transfer. (See Marcus *et al.* 1967 for a discussion.)

As can be noted from the present and previous studies (Winters *et al.* 1967b; Mori *et al.* 1968) a combination of gross behavior, ongoing EEG, averaged evoked responses and multiple unit activity form a useful group of neuropharmacological techniques for the analysis of drug-induced states in cats with chronic brain electrode implants.

SUMMARY

The EEG, gross behavior and multiple unit activity were recorded during the continuous progression of states induced by amphetamine (*d*-, and meth-), lysergic acid diethylamide (LSD-25), mescaline, gamma-hydroxybutyrate, pentylenetetrazol or phencyclidine. The drugs appear to fall within a pattern of progressively increasing excitatory states. The least active agents induce only the initial phase, *i.e.*, excited: amphetamine; then hallucinoid: LSD-25 and mescaline. The more potent agents transcend these initial phases and induce generalized seizures: gamma-hydroxybutyrate, phencyclidine and pentylenetetrazol. The reticular multiple unit activity increased slightly during the initial two phases; then following gamma-hydroxybutyrate the basal level fell progressively while the fluctuation rose markedly, whereas following pentylenetetrazol the multiple unit activity progressively increased. During the generalized seizures the unit activity was markedly elevated in both of these groups; then the unit activity fell during the brief period of post-ictal depression followed by a return of each drug group to the unit activity levels noted during the pre-seizure state.

RÉSUMÉ

ACTIVITÉ UNITAIRE MULTIPLE DE LA FORMATION RÉTICULAIRE AU COURS D'UNE PROGRESSION D'ÉTATS INDUITS PAR DES EXCITANTS DU SYSTÈME NERVEUX CENTRAL

L'EEG, le comportement global et l'activité unitaire multiple ont été enregistrés pendant la progression continue d'états induits par: les amphétamines (*d* et meth), l'acide diéthylamide lysergique (LSD-25), la mescaline, le gamma-hydroxybutyrate, le pentylènetétrazol ou phency-

clidine. Ces drogues provoquent des états d'excitation progressivement croissants. Les agents les moins actifs induisent seulement la phase initiale, c'est-à-dire l'excitation (amphétamines) puis des hallucinations (LSD-25 et mescaline). Les agents les plus puissants dépassent ces phases initiales et induisent des crises généralisées (gamma-hydroxybutyrate, phencyclidine et pentylènetétrazol). L'activité unitaire multiple réticulaire augmente légèrement pendant les deux phases initiales; puis, après gamma-hydroxybutyrate, le niveau de base tombe progressivement tandis que la fluctuation augmente de façon marquée; après pentylènetétrazol l'activité unitaire multiple augmente progressivement. Pendant les crises généralisées, l'activité unitaire s'élève de façon importante dans ces deux groupes, puis elle diminue pendant la brève période de dépression post-ictale, qui est suivie par un retour, pour chaque groupe de drogues, aux niveaux d'activité unitaire notés pendant l'état pré-critique.

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