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Effects of Cocaine on Propagation of Limbic Seizure Activity

HENRY LESSE AND JEREMIAH P. COLLINS

Department of Psychiatry and Biobehavioral Sciences, The Neuropsychiatric and Brain Research Institutes, School of Medicine, University of California, Los Angeles, Los Angeles, CA 90024

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LESSE, H. AND J. P. COLLINS. *Effects of cocaine on propagation of limbic seizure activity*. PHARMAC. BIOCHEM. BEHAV. 11(6) 689–694, 1979.—Effects of cocaine on the spread of epileptiform discharges within the limbic system were studied in cats prepared with bilateral arrays of indwelling electrodes. Low frequency focal electrical stimulation at threshold intensity was employed to initiate after-discharges in the hippocampus and amygdala. Latencies for the propagation of epileptiform activity to distant limbic sites were determined. Saline and drug tests were alternated, with 96-hr intervals between cocaine administrations. Three subconvulsant doses (1–10 mg/kg cocaine hydrochloride, injected intramuscularly) were tested in a counterbalanced order. Cocaine administration significantly increased the speed at which epileptiform discharges spread to the amygdala and to the hippocampus. This effect was dose-related, it followed both hippocampal and amygdalar stimulation and was evident in ipsilateral as well as contralateral projection sites. These changes were found when limbic seizure patterns were localized and also after fully developed motor convulsions were evoked. In addition, cocaine decreased the duration of the propagated discharges. These results suggest that subconvulsive doses of cocaine have an excitatory effect on the hippocampus and amygdala, increasing their sensitivity to repetitive discharges originating in distant sites. A concurrent inhibitory effect is suggested by the decreased duration of the propagated discharges

Cocaine Limbic system Hippocampus Amygdala Seizure propagation
Limbic seizure discharges Temporal lobe epilepsy Cat

IN ADDITION to its effects as a psychomotor stimulant and a local anesthetic, cocaine has both anticonvulsant and convulsant properties. The drug suppresses generalized motor convulsions induced by electroshock [28,29], pentylenetetrazol [29], hyperbaric oxygen [20], and audiogenic seizures [4]. However, in high doses, cocaine acts as a convulsant rather than a anticonvulsant. This effect has been well known since the turn of the century when generalized seizures were observed in humans receiving cocaine as a therapy for morphine addiction [5]. Cocaine seizures also were reported in a variety of laboratory animals [9, 30, 31]. More recently, it was suggested that cocaine preferentially activates the limbic system. High doses of cocaine induced prominent changes in the rhythmic electrical activity of the amygdala and pyriform cortex which progressed to seizure discharges, then spread to other subcortical structures and to the neocortex and finally culminated in generalized motor convulsions [10,11].

We recently reported that subconvulsant doses of cocaine significantly decreased the stimulating current required to evoke focal after-discharges in the hippocampus and the amygdala but not in the septal region [22]. However, it is well known that local and 'projected' epileptiform processes differ substantially and drugs may have different effects on the seizure activity occurring in projection sites [1,8]. Therefore, the present experiments examine the extent to which the cocaine-induced changes in excitability to local electrical stimulation may also apply to the sensitivity of these limbic structures to repetitive discharges originating in synaptically related, distant sites. The purpose of the present experiments was to study the effects of different subconvulsant doses of cocaine on the spread of epileptiform discharges to a series of projection sites in the hippocampus and the amygdala. We investigated the possibility that cocaine, in addition to lowering thresholds for direct electrical stimulation, also facilitates the propagation of seizure activity within the limbic system.

METHOD

Subjects

Subjects were seven adult female cats weighing between 2.5 and 3 kg. Under pentobarbital anesthesia, they were prepared surgically with indwelling stainless steel electrodes. Arrays of bipolar needle and concentric electrodes with 1 mm separation between tips were implanted bilaterally in the dorsal hippocampus and the baso-lateral portion of the amygdaloid nucleus. Four electrodes in each structure were employed for simultaneous electrical stimulation and recording. The following stereotaxic coordinates from the Jasper and Ajmone Marsan atlas [19] were used: hippocampus A3: H+6, +7; L5, 6, 7, amygdaloid nucleus A 12.5; H −5, −6; L8, 9, 10. Epidural electrodes were implanted bilaterally over the occipital cortex. A stainless steel screw was placed in the frontal sinus for use as a reference electrode and a

series of interconnected screws fixed to the skulls served as a ground electrode. The electrode leads terminated at a miniature connector attached to the skull with dental acrylic. At least three weeks were allowed for post-operative recovery before any experiments were initiated.

Apparatus

During test sessions cats were placed in an electrically-shielded, sound-attenuating chamber equipped with a one-way viewing mirror, bar-press and milk delivery apparatus. Recordings of subcortical and neocortical activity were obtained with a 16 channel Grass polygraph and occasionally were stored on magnetic tape. Brain stimulation was provided by a Grass square wave stimulator and a constant current unit. A dual beam oscilloscope was employed for continuous monitoring of current and voltage.

Procedures

Cats were trained to bar press for milk reinforcement. A 23-hr period of food deprivation preceeded test sessions which were conducted while the subjects were bar pressing. This procedure provided a stable level of arousal and an activated EEG pattern during the induction of after-discharges by focal limbic stimulation.

Brain Stimulation and recordings. Rectangular, monophasic pulses (3 Hz, 0.5 msec duration) applied between adjacent electrode tips were employed for brain stimulation. Current was adjusted to threshold intensity for focal after-discharges (AD) during all test sessions since supramaximal stimulations may alter propagation patterns. With the use of low frequency stimulation, electrophysiological responses could be recorded from points adjacent to the stimulating electrode during the 333 msec intervals between pulses; thus, the initiation of the AD was detected while brain stimulation was occurring. Electrophysiological recordings were obtained between the bipolar electrodes and also between individual electrode tips in each structure and the common sinus reference.

AD threshold determinations were conducted for both hippocampal and amygdalar stimulation sites in each subject employing a method that has been described previously [23]. In brief, stimulation was applied at one minute intervals with 10% increments in current until self-sustaining focal ADs were evoked. Pulse trains of standard 30 sec duration were terminated sooner following the evocation of AD activity in sites adjacent to the stimulating electrode. These determinations were repeated at 48 hr intervals until stable thresholds were obtained (i.e., there was no more than a 10% variation for three successive test sessions). Latencies for the propagation of seizure activity were determined using electrographic tracings recorded at a speed of 30 mm/sec. Time intervals were measured from the initiation of self-sustaining AD in the structure stimulated to the onset of rhythmic epileptiform activity persisting for at least two seconds in each of the projection sites.

Saline and cocaine testing. After the establishment of stable AD threshold levels, a series of alternating saline and cocaine tests was initiated. These test sessions were always separated by at least 48 hours and the cocaine administrations by at least 96 hr. Cocaine hydrochloride was injected intramuscularly in a concentration of 50 mg/ml as the base. Low, medium and high doses were tested in a counter-balanced order across subjects. Based upon preliminary experiments, intramuscular injections of 2.5, 5, 10 mg/kg were selected to represent a wide range of subconvulsant doses, with the 10 mg/kg injection just below the level required to induce localized limbic seizure activity in most cats. In the present experiments, focal seizure activity beginning in the amygdala occasionally followed the 10 mg/kg cocaine injection and in these instances the low, medium and high test doses were adjusted to 1, 2.5 and 5 mg/kg. EEG recordings were monitored continuously following all drug administrations. Thirty minutes after the injection of either cocaine or saline, focal after-discharges were evoked by threshold currents using the stimulation method described above and latencies for propagated discharges were measured. The three cocaine doses and the saline injections were tested twice with amygdalar (A) and twice with hippocampal (H) stimulations. Thus, there were 12 cocaine tests for each subject. The initial structure receiving focal stimulation was varied across subjects so that the sequence of testing was either A-H-A-H or H-A-H-A. With this procedure, the effects of alternate cocaine and saline tests were compared as limbic seizure development progressed. The overall duration of the experimental program was between 3.5 to 5 months for individual subjects (5–9 weeks for baseline electrical recordings and AD thresholds; 9–13 weeks for subsequent drug and saline testing).

At the conclusion of the experiments, subjects were deeply anesthetized and brains were perfused with saline and 15% Formalin. The location of all electrode tips was identified microscopically in stained serial sections.

RESULTS

A mean of 7 stimulation sessions was required to attain stable AD thresholds for both amygdalar and hippocampal stimulation. Some subjects received several additional stimulations to obtain interhemispheric propagation before the drug testing was initiated. Cocaine administration resulted in marked reductions in time between the initiation of after-discharges (AD) in the stimulated structure and the appearance of epileptiform discharges in distant limbic structures. This effect followed both hippocampal and amygdalar stimulation, occurred with each dose level tested and was evident in ipsilateral as well as contralateral projection sites. The drug-induced decreases in latency for the onset of propagated discharges were found during the early stages of seizure development when epileptiform patterns remained localized to limbic structures. Similar effects also occurred later during the second series of test sessions when focal stimulation frequently evoked cortical seizure patterns and fully developed motor convulsions (i.e., 'kindled seizures' [18]).

These effects are illustrated in Figs. 1 and 2. The upper tracings of Fig. 1, obtained following a saline injection, show typical after-discharges elicited by electrical stimulation of the dorsal hippocampus and the gradual spread of epileptiform activity to distant sites. The AD activity, evoked in the left hippocampus during electrical stimulation, persists following the termination of stimulation. Subsequently, paroxysmal discharges appear at distant limbic sites; first in the contralateral hippocampus, then in the ipsilateral amygdala and finally in the contralateral amygdala. These discharges, occurring at different frequencies in the hippocampus and amygdala, terminate abruptly. Subsequent postictal depression of activity is evident in recordings from the affected structures. Propagation to the neocortex was absent

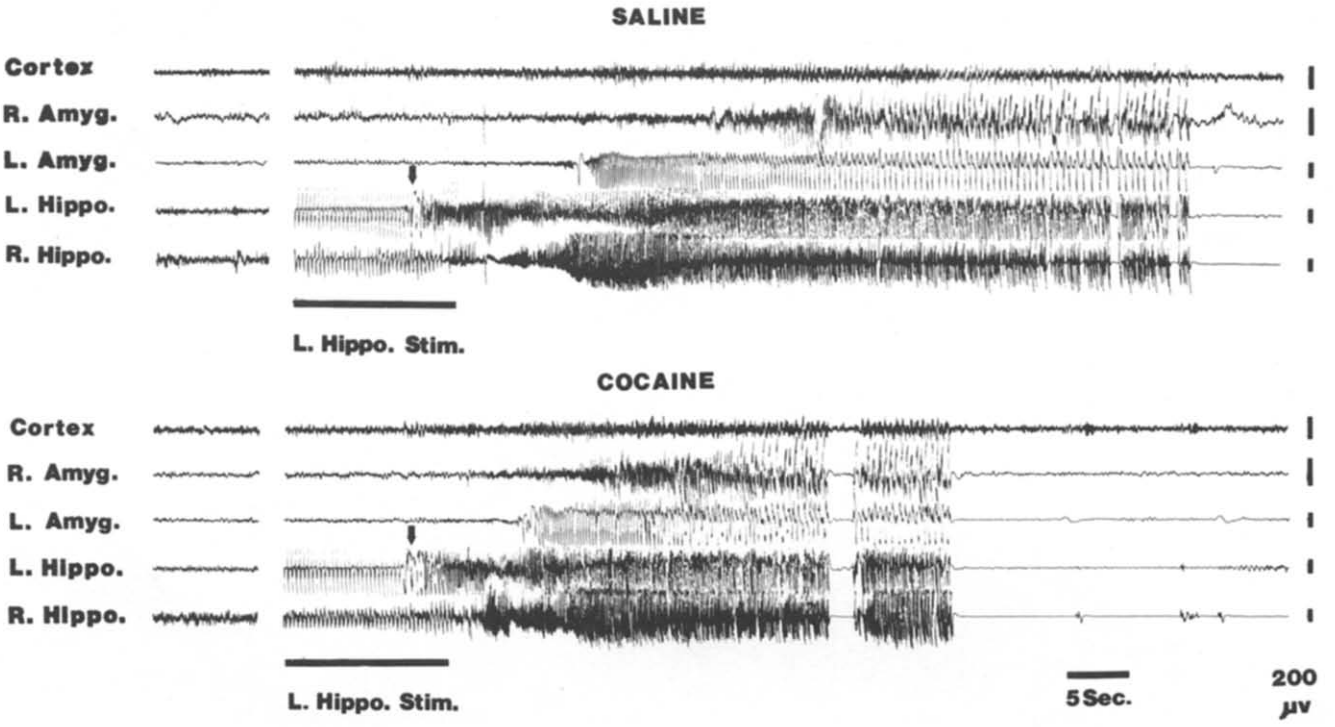

FIG. 1. Effects of saline (upper tracings) and cocaine, 5 mg/kg IM (lower tracings) on propagation of epileptiform activity after electrical stimulation of left dorsal hippocampus. Note decrease in latency for appearance of seizure discharges in each projection site (right dorsal hippocampus, left basolateral amygdala, right amygdala) after cocaine administration.

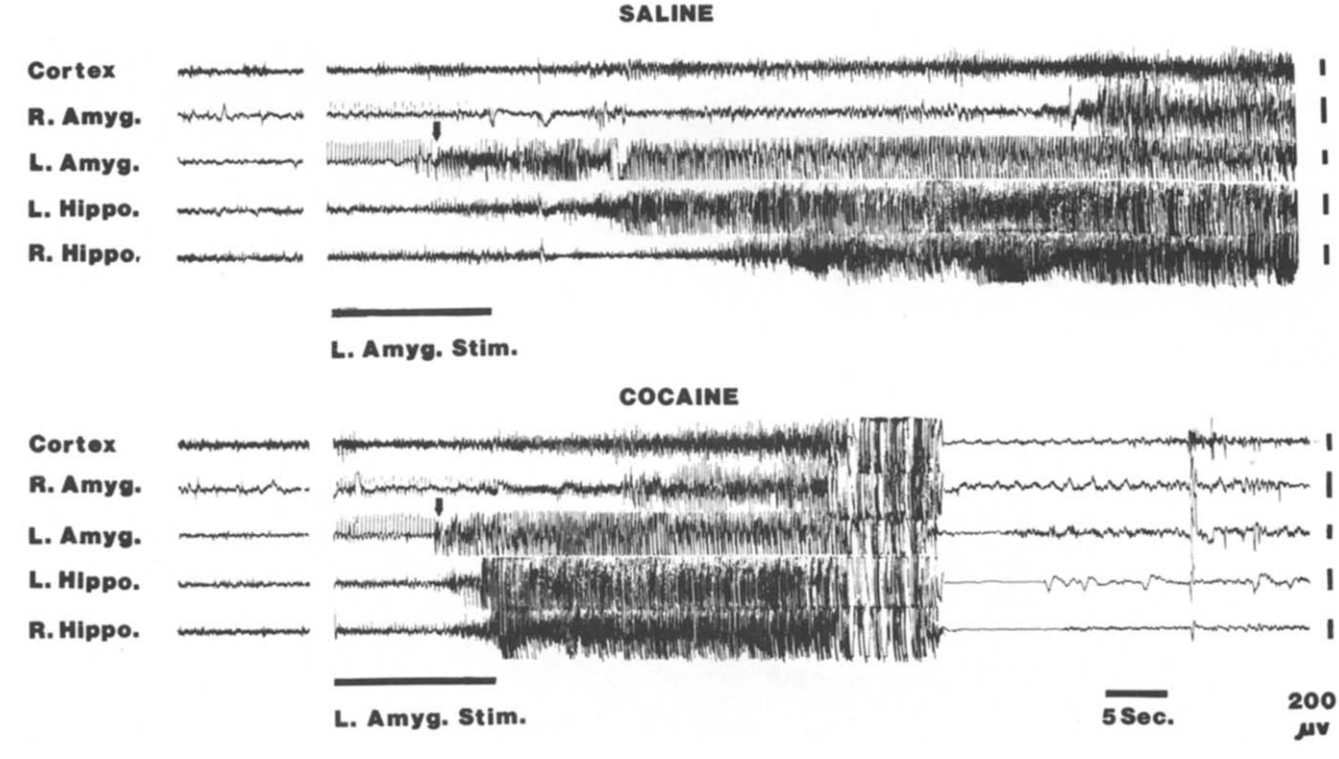

FIG. 2. Effects of saline (upper tracings) and cocaine, 5 mg/kg IM (lower tracings) on propagation of epileptiform activity after electrical stimulation of left basolateral amygdala. Note accelerated propagation to limbic projection sites and to neocortex and the decreased duration of the ictal episode.

at this stage of testing and no motor convulsions occurred. The cat responded to stimulations with automatisms characteristic of limbic seizures, (i.e., contraversive head turning and brief mouth movements).

The lower tracings were obtained during the subsequent test session after the cat had received 5 mg/kg of cocaine. The sequence of the appearance of paroxysmal discharges in the contralateral hippocampus, ipsilateral and contralateral amygdala remains unchanged. However, the time of onset of the discharges in each of these projection sites now is markedly decreased. In addition, the duration of the ictal episode is diminished.

Recordings from another subject following stimulation of the basolateral amygdala are displayed in Fig. 2. The upper tracings, obtained during a saline test, show relatively prolonged after-discharge activity (approximately 15 sec are omitted). The AD is initiated in the left amygdala; propagated discharges appear first in the ipsilateral hippocampus. In this subject, epileptiform discharges eventually involve the neocortex and a generalized motor convulsion occurred. As illustrated in the lower tracings, cocaine administration again decreases the latency for spread of paroxysmal activity to all secondary sites. The duration of the epileptiform activity diminishes in all sites. It should be noted that for illustration purposes, tape recordings of electrophysiological activity were replayed at a slow speed (6 mm/sec) in order to display complete ictal events. However, all measurements of latency were conducted with a 30 mm/sec recording speed.

Table 1 summarized the results of the saline and drug tests for all subjects. The mean latencies represent the time in seconds from the induction of AD in the stimulated structure to the appearance of epileptiform discharges in each secondary site. As shown in Table 1, propagation latency to secondary sites decreased following each cocaine dose. These latencies were reduced as much as 83% after hippocampal stimulation and 90% after amygdala stimulation. An analysis of variance was performed comparing the effects of saline and the low, medium and high doses of cocaine. With hippocampal stimulation, the reductions in propagation latency were significantly dose-related for the contralateral hippocampus (CH), $F(3,18)=9.7$, $p<0.001$; ipsilateral amygdala (IA), $F(3,18=16.4$, $p<0.001$; and contralateral amygdala (CA), $F(3,18)=23.2$, $p<0.001$. Cocaine also reduced latencies when the amygdala was stimulated. Propagation latency to both the ipsilateral and contralateral hippocampus showed significant dose-related decreases; $F(3,18)=5.9$, $p<0.01$; $F(3,18)=10.3$, $p<0.001$. In addition, the dose-effect was significant for the contralateral amygdala $F(3,18)=12.8$, $p<0.001$. The lowest dose level tested (1–2.5 mg/kg) proved effective in reducing propagation time with both hippocampal and amygdala stimulation (Student's t test, $p<0.001$). Differences between the drug-induced reductions in interhemispheric and intrahemispheric propagation and differences between hippocampal and amygdala stimulations were nonsignificant. The drug-induced changes in latency were similar for the first and the second series of test $F(1,38)=0.02$, $p>0.8$.

In addition to accelerating the speed of propagation, cocaine administration also reduced the duration of seizure discharges. The mean durations (in sec) of epileptiform activity in the secondary sites are shown in Table 2. Analysis of variance indicated that there were significant dose effects at all projection sites with both hippocampal stimulation CH, $F(3,18)=10.8$, $p<0.001$; IA, $F(3,18)=8.9$, $p<0.001$; CA, $F(3,18)=7.4$, $p<0.01$, and with amygdalar stimulation CA, $F(3,18)=4.2$, $p<0.025$; IH, $F(3,18)=5.1$, $p<0.025$, and CH, $F(3,18)=3.3$, $p<0.05$. The duration of epileptiform discharges after saline injections increased during the second series of tests and the cocaine-induced decrease in duration was proportionately greater as indicated by a series-by-dose interaction, $F(3,156)=36.4$, $p<0.001$.

Test sessions were always initiated while limbic seizures were localized. Generalized motor convulsions developed at various times in different cats; in some animals only at the conclusion of the second series of alternating drug and saline tests. Thus, data on diffuse propagation to the cortex was limited, since generalized motor convulsions were induced during only 26% of the tests in the first series (22/84) and 77% of tests in the second series (65/84). Moreover, neocortical seizure patterns tended to appear gradually after a focal stimulation and, in some subjects, it was difficult to measure accurately the time of onset of these propagated discharges. The effects of cocaine on motor convulsions and on the

TABLE 1

MEAN LATENCY (SEC) FOR APPEARANCE OF EPILEPTIFORM DISCHARGES IN SECONDARY SITES FOLLOWING COCAINE ADMINISTRATIONS

	Hippocampus Stimulated		
	*CH	IA	CA
Saline	8.2 ± 1.4†	11.4 ± 1.9	19.3 ± 3.0
Low Dose	4.3 ± 1.1	6.7 ± 1.7	9.8 ± 2.2
Medium	3.7 ± 0.9	4.9 ± 1.1	7.8 ± 1.3
High	1.5 ± 0.6	3.2 ± 0.7	4.4 ± 1.0
	Amygdala Stimulated		
	CA	IH	CH
Saline	10.3 ± 1.7	4.4 ± 1.2	16.0 ± 3.2
Low Dose	5.5 ± 0.7	3.6 ± 1.1	10.3 ± 3.7
Medium	3.6 ± 0.7	2.5 ± 0.9	6.4 ± 2.1
High	3.0 ± 0.7	0.4 ± 0.3	4.1 ± 1.1

*Contralateral Hipocampus, Ipsilateral Amygdala, Contralateral Amygdala, Ipsilateral Hippocampus.
†Means ± SEM.

TABLE 2

MEAN DURATION (SEC) OF EPILEPTIFORM DISCHARGES IN SECONDARY SITES FOLLOWING COCAINE ADMINISTRATIONS

	Hippocampus Stimulated		
	CH	IA	CA
Saline	85.8 ± 15.3†	82.7 ± 15.4	78.8 ± 14.6
Low Dose	53.9 ± 5.1	51.5 ± 4.4	48.4 ± 3.1
Medium	39.6 ± 4.8	38.4 ± 4.1	35.6 ± 3.7
High	32.9 ± 3.6	32.2 ± 3.8	31.0 ± 3.1
	Amygdala Stimulated		
	CA	IH	CH
Saline	62.2 ± 13.7	68.1 ± 14.2	56.0 ± 13.6
Low Dose	45.8 ± 5.4	47.6 ± 5.8	40.8 ± 6.8
Medium	36.2 ± 3.3	37.3 ± 3.5	33.5 ± 4.0
High	29.4 ± 3.6	31.9 ± 3.8	28.3 ± 3.8

†Means ± SEM.

propagation of seizure discharges to the neocortex was variable. In two subjects, cocaine suppressed motor convulsions. In one cat, only one generalized motor convulsion was induced during six successive cocaine tests; while generalized convulsions followed each of the six alternating saline tests. In another animal, there were no generalized convulsions during any cocaine test although motor seizures were induced in 11 of the 12 alternating saline tests. Four other cats regularly responded to focal limbic stimulation with generalized convulsions during the second series of tests. In these subjects motor convulsions occurred following all cocaine administrations and the cortical seizure patterns and motor convulsions appeared more rapidly following cocaine administration. An example of this effect is seen in Fig. 2.

DISCUSSION

As indicated by the mean latency values listed in Table 1 and the electrographic recordings in Figs. 1 and 2 there were distinct differences in the sequence of propagation following stimulation of the amygdala and the hippocampus. With amygdalar stimulation, seizure discharges regularly appeared in the ipsilateral hippocampus before interhemispheric spread occurred. In contrast, following hippocampal stimulation, the preferential pattern involved propagation to the contralateral hippocampus prior to the appearance of discharges in the ipsilateral amygdala. These results are consistent with the observations of one earlier report [3] but at variance with another [32]. Cocaine administrations did not alter these preferential patterns.

The present finding that cocaine significantly accelerated the spread of seizure discharges to the hippocampus and amygdala is consistent with our previous report that the drug lowered the current threshold required to evoke afterdischarges during direct electrical stimulation [22]. The present results suggest that subconvulsant doses of cocaine have an excitatory effect on limbic structures, increasing their sensitivity to neuronal discharges arising in distant brain sites and increasing their tendency to respond with repetitive discharges. This change in excitability may contribute to the marked augmentation of 40 Hz rhythmic activity of the amygdala observed following cocaine administration [11, 12, 13, 17]. This fast rhythmic electrographic pattern is characteristically recorded form the amygdala in response to a variety of environmental stimuli [21]. In addition, this effect may help to account for the activation by cocaine of pre-existing limbic seizure foci in patients with temporal lobe epilepsy [14]. The present findings are also consistent with previous reports that high doses of cocaine induce convulsions and generalized seizure patterns which begin in limbic structures [11, 12, 13].

In contrast to the facilitating effect of cocaine on the spread of seizure discharges, a decrease in the duration of these propagated discharges was also found. A similar decline in the duration of AD in limbic sites receiving direct electrical stimulation occurs [22]. These changes suggest an inhibitory action affecting mechanisms responsible for the maintenance of self-sustained ictal discharges. Since convulsant or anticonvulsant properties of cocaine are typically assigned to high or low doses, it is interesting to note that in the present experiments the same doses facilitated the spread of seizure patterns, decreased AD threshold and also decreased the duration of seizure discharges (effects that might be interpreted as both anticonvulsant and convulsant). The lowest dose level tested (1–2.5 mg/kg), resulted in significant changes in these electrophysiological responses. Moreover, the intensity of each of these effects increased at the highest test dose, which approached convulsant threshold for the cat.

The seemingly paradoxical findings of a facilitation of propagation, suggesting an excitatory effect; accompanied by a decrease in the duration of seizure activity, suggesting an inhibitory effect may be resolved if the actions of cocaine affect independent neural mechanisms responsible for initiating and for maintaining self-sustaining repetitive discharges. These results appear less paradoxical when changes in the temporal characteristics of the entire ictal event are considered. Cocaine appeared to compress the ictal episode. The paroxysmal activity spread more rapidly to distant subcortical projection sites and the seizure pattern(whether localized or generalized) appeared to reach its maximum topographic distribution, amplitude and frequency more rapidly. The characteristic signs of impending termination (a progressive decline in the frequency of discharges with brief periods of electrical silence) appeared sooner and postictal depression occurred more rapidly. It is generally held that the refractory periods of neurons progressively lengthen as increasing neuronal aggregates become involved in repetitive discharges and the termination of an ictal episode approaches. A variety of neurophysiological studies [7] tend to support the well known conclusion that "each epileptic discharge carries within it the makings of its own end, for this will supervene as soon as fatigue increases to a point where inexcitability is absolute" [16]. Thus the observed decrease in the duration of ictal episodes may be inextricably bound to excitatory effects of cocaine which facilitate the spread of limbic seizure activity. Many of the known actions of cocaine could lead to synaptic, or to nonsynaptically generated, changes in excitation which might facilitate the spread of epileptiform discharges within the limbic system. These include actions on membranes interfering with transient increases in permeability to sodium and release of calcium [2,26], as well as the actions of cocaine on various neurotransmitters including dopamine [15], serotonin [25,27], norepinephrine [6,33] and acetylcholine [24].

The present results provide evidence suggesting that cocaine, even in low subconvulsant doses, has potent effects in modifying the excitability of the hippocampus and the amygdala. These findings are especially interesting because of the diffuse anatomic projections of these limbic structures and the large body of experimental and clinical data indicating their functional importance in the regulation of emotion and information processing.

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