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Differential Effects of Cocaine on Limbic Excitability

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LESSE, H. AND J. P. COLLINS. *Differential effects of cocaine on limbic excitability*. PHARMAC. BIOCHEM. BEHAV. 13(5) 695–703, 1980.—Effects of cocaine on the initiation and maintenance of electrically induced limbic afterdischarges (AD) were studied in cats. Current thresholds for evoking AD in the hippocampus, amygdala and septal region were determined following alternating saline and cocaine administrations. Three subconvulsant doses (1–10 mg/kg, IM) were tested at 96 hour intervals. The cocaine administrations significantly decreased the current required to initiate AD in both the hippocampus and amygdala. This effect was dose-related; it was found when limbic discharges were localized and also after fully developed motor convulsions were evoked. By contrast, septal AD thresholds were unchanged. In addition, dose-related reductions in AD duration were induced at all limbic sites tested. Restrictions in propagation to distant sites occurred during early stages of seizure development. Progressive changes did not develop following either repeated tests of single-dose effects or during a six week period of daily cocaine administration. These results suggest that cocaine has preferential excitatory effects on closely related limbic structures, increasing the sensitivity of the hippocampus and amygdala to direct electrical stimulation. A concurrent, independent inhibitory action is implied by the reduced duration of limbic afterdischarges. The absence of progressive electrophysiological responses suggests that there is no potentiation of limbic excitatory effects following the repeated administration of doses which do not induce focal epileptiform activity.

Cocaine Limbic system Focal brain stimulation Hippocampus Amygdala Septal region
Afterdischarge thresholds Temporal lobe epilepsy Kindling Cocaine sensitization Cat

COCAINE-INDUCED convulsions have been recognized since the turn of the century when they were first observed in patients receiving cocaine as a therapy for morphine addiction [5]. These convulsant properties of cocaine, a subject of continuing clinical and research interest, were considered to be a manifestation of the drug's action as a central nervous system stimulant. Based on observation of seizures and deaths associated with respiratory failure, it was inferred that cocaine "first acts on the cerebral cortex," and then, somehow, "stimulation proceeds from above downward" to medullary centers. This quaint explanation of the central nervous system actions of cocaine persists in pharmacological textbooks and in contemporary reviews [7,23]. However, anticonvulsant, as well as convulsant, properties of the drug have been reported [4, 28, 33, 34, 51]. Moreover, the convulsions induced by high doses of cocaine begin with limbic seizure discharges [12,13] and the drug accelerates the propagation of epileptiform activity to hippocampal and amygdalar projection sites [33].

Although these reports suggest that cocaine may preferentially activate the limbic system, there has been a surprising lack of investigations applying neurophysiological methods in systematic examination of changes in the excitability of limbic system components. The purpose of the present study was to investigate differential effects of cocaine on the sensitivity of the amygdala, hippocampus and septal region to direct electrical stimulation. The current threshold for the elicitation of focal afterdischarges was employed as an indicator of the excitability of selected limbic sites to direct electrical stimulation. A wide range of subconvulsant doses of cocaine was then tested for differential effects on both the initiation and maintenance of self-sustained repetitive afterdischarges. Progressive changes in limbic excitability following repeated administration were also explored, because possible chronic neurophysiological effects of the drug are unknown and both tolerance and sensitization phenomena have been reported for cocaine-induced alterations of behavior [8, 11, 49, 51, 53, 55, 58]. Some of the present results have been summarized in a preliminary report [34].

METHOD

Subjects

Subjects were thirteen adult female cats weighing between 2.5 to 3 kg. Under pentobarbital anesthesia, they were prepared with indwelling stainless steel electrodes. In ten subjects, arrays of 0.25 mm bipolar needle and concentric electrodes with 1 mm separation between the exposed tips, were implanted bilaterally in the dorsal hippocampus and the basolateral amygdala. In three subjects, electrodes were

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placed in the septal region and the caudate nucleus. Two bipolar electrodes in each structure were employed for simultaneous electrical stimulation and recording. The following stereotaxic coordinates from the Jasper and Ajmone Marsan atlas [25] were used: hippocampus A3; H+6, +7; L5, 6, 7, amygdala A12.5; H−5, −6; L8, 9, 10, septal region A16; H+1, +2; L1.5; caudate nucleus A16, 18; H+5, +6; L5, 6. Epidural electrodes were implanted bilaterally over the occipital cortex. A stainless steel screw placed in the frontal sinus served as a reference electrode and a series of interconnected screws fixed to the skull provided 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 postoperative recovery before experiments were initiated.

Apparatus

During test sessions, subjects were placed in an electrically-shielded, sound-attenuating chamber equipped with a one-way mirror, bar-press and milk delivery apparatus. Recordings of subcortical and neocortical activity were obtained with a 16 channel Grass polygraph and stored on magnetic tape. Brain stimulation was provided by a Grass square wave stimulator and constant current unit. A dual beam oscilloscope was employed for the continuous monitoring of current and voltage. A cumulative recorder registered bar-pressing responses. Signal markers were employed to coordinate brain stimulations with recordings of behavioral and electrophysiological responses.

Procedures

All cats were trained to bar-press for milk reinforcement. A 23-hour period of food deprivation preceded test sessions which were conducted while the subjects were bar-pressing. This procedure provided both a stable level of arousal and an activated EEG pattern during the induction of afterdischarges by focal limbic stimulation.

Brain stimulation and recordings. Low frequency electrical stimulation with rectangular, monophasic, 0.5 msec pulses applied between adjacent electrodes was employed for limbic AD threshold tests. For the hippocampus and amygdala, 3 Hz stimulation was used. Since AD were not induced in the septal region by 3 Hz stimulation at currents below 3 mA, the frequency was adjusted to 9 Hz to provide current thresholds similar to those of the hippocampus and amygdala (although septal coulomb thresholds were higher). With use of low frequency stimulation, electrophysiological responses were recorded during the intervals between pulses, from points adjacent to the stimulating electrode and from projection sites in related structures. Thus, the initiation of AD was detected while brain stimulation was occurring and even brief discharges were detected. The induction of AD in the caudate required both high frequencies and high currents. In each subject, electrophysiological recordings were obtained between both the bipolar electrodes and individual electrode tips in each structure and the common sinus reference.

AD threshold determinations were conducted for selected stimulation sites in each subject employing a previously described method [32,35]. In brief, stimulation was applied at one minute intervals; 10% increments in current were employed until self-sustaining focal AD were evoked. Thirty second pulse trains were terminated when AD were evoked in sites adjacent to the stimulating electrode. The AD threshold was defined as the minimal current required to evoke self-sustaining afterdischarges persisting for at least one second after stimulation was terminated. These determinations were continued at 48 hour intervals until stable threshold values were obtained (i.e., there was no more than a 10% variation for three successive test sessions). Electrographic tracings recorded at a speed of 30 mm/sec were employed for AD duration measurements.

Saline and cocaine testing. After stable AD threshold levels were obtained, a series of alternating saline and cocaine tests was initiated. Saline and drug test sessions were always separated by at least 48 hours and the cocaine administrations by at least 96 hours. Cocaine hydrochloride was injected intramuscularly in a concentration of 50 mg/ml as the base. Low, medium and high doses were tested in a varied order, counterbalanced across subjects. Based upon our preliminary experiments, intramuscular injections of 2.5, 5, and 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 subjects. In the present experiments, focal seizure activity beginning in the amygdala occasionally followed the 10 mg/kg cocaine injection. In both instances, the low, medium and high test doses were adjusted to 1, 2.5 and 5 mg/kg. Electrophysiological recordings were monitored continuously following all cocaine administrations to detect possible drug-induced epileptiform activity.

Thirty minutes after the injection of either cocaine or saline, AD thresholds were determined using the stimulation method described above. Initial current intensity was set 50–60% below the previously determined threshold for each electrode site. The low, medium and high cocaine doses which were alternated with saline injections were tested at least twice at each limbic stimulation site. Thus, there were at least 12 cocaine tests for each subject. The initial structure receiving focal stimulation was varied across subjects so that the sequence of testing for amygdalar (A) or hippocampal (H) stimulations was either A-H-A-H or H-A-H-A. A third and fourth series of drug tests were subsequently conducted with four of these seven subjects. With this procedure, the effects of alternate cocaine and saline tests were compared as limbic seizure development (i.e., 'kindling') gradually progressed. Since seizure development is slow in the cat—generally requiring about 25 amygdalar or 40 hippocampal stimulations before kindled seizures are evoked [22,56]—drug effects were tested at early and late stages of kindling. Thus, at the onset of the first drug test series, limbic stimulations characteristically evoked only brief, localized epileptiform discharges with minimal behavioral reactions (stage 1 seizures). Ictal episodes progressed in duration and severity and fully developed motor convulsions were evoked regularly during the third and fourth series.

Since evidence of tolerance or sensitization phenomena was not found during the four series of repeated 96 hour single-dose tests, the possibility that daily cocaine administration might result in progressive excitability changes was investigated. Hippocampal AD thresholds were tested in a group of three cats never exposed to cocaine. The initial effects of a 5 mg/kg "test dose" of cocaine and a saline control injection were then determined. Subsequently, 2.5 mg/kg "maintenance doses" of cocaine were administered intramuscularly twice a day at approximately 800 and 1700 hours, five days per week, for a six week period. At the end of the first week, the 5 mg/kg "test dose" of cocaine was substituted for the morning maintenance injection; electro-

graphic activity was monitored for 30 minutes and then the hippocampal AD threshold was retested. Each Monday morning (after a two day, drug-free period) saline was injected and the AD threshold was determined. This procedure of alternating cocaine and saline tests was repeated at the end of the second, third, fourth, fifth and sixth week of daily cocaine administrations. The 42 tests were analyzed for evidence of progressive changes in AD threshold and AD duration.

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

RESULTS

Effects of Cocaine on Afterdischarge Thresholds

There was a precipitous reduction in AD threshold during the first few baseline stimulations, followed by a negatively accelerating decline after successive tests and rapid stabilization at a new level. A mean of seven sessions was required to obtain stable thresholds for both amygdalar and hippocampal sites. Initially, the minimal current required to evoke AD in the amygdala and the hippocampus was similar (means = 1.40 mA vs. 1.39 mA). By the time stable thresholds were obtained, however, amygdalar thresholds were significantly lower (0.53 mA vs. 0.94 mA; $p<0.03$, Student's t-test). There was no further progressive decline in current threshold throughout the experimental period although the development of electrophysiological seizure patterns and convulsive behaviors continued during the first two test series culminating in generalized motor convulsions in all subjects during the third series.

Saline injections did not affect AD thresholds and the results of the first and second series of saline tests were similar. Cocaine administrations, however, resulted in significant reductions in the minimal current required to evoke afterdischarges. This effect followed both hippocampal and amygdalar stimulation in all subjects and occurred with each dose level tested. Septal AD thresholds, however, were not affected by cocaine. Threshold reductions were significantly dose related for both hippocampus and amygdala, $F(3,36)=7.8$, $p<0.001$. These drug-induced changes were found during the early stages of seizure development, when AD remained localized to limbic structures and the behavioral effects of focal stimulation were limited to automatisms (e.g., brief arrest reactions or contraversive head turning, and mouth movements). Similar effects occurred later, during the second series of tests, when limbic stimulations frequently evoked diffusely propagated seizure patterns and motor convulsions. The drug-induced threshold reductions persisted in subjects receiving a third and fourth series of tests when fully developed motor convulsions (kindled seizures) were always evoked.

Table 1 summarizes the results of saline and cocaine tests for all subjects. Mean thresholds represent the minimal current in mA for the induction of AD in the structure stimulated. As illustrated in Table 1, hippocampal and amygdalar AD thresholds decreased following each cocaine dose. Thresholds were reduced as much as 38% following hippocampal stimulation and 23% after amygdalar stimulation.

An analysis of variance comparing the effects of saline and low, medium and high doses of cocaine indicated that the reductions in AD threshold were significantly dose-related with hippocampal stimulation, $F(3,18)=4.7$, $p<0.02$ and also with amygdalar stimulation, $F(3,18)=7.5$, $p<0.01$. Although larger reductions in hippocampal AD threshold occurred with each of the three test doses, these differences did not reach statistical significance when all tests were compared. Cocaine administrations had no significant effect on septal AD thresholds (see Table 1).

TABLE 1

MEAN AFTERDISCHARGE THRESHOLD (MA) FOLLOWING COCAINE ADMINISTRATIONS

	Hippocampus	Amygdala	Septal region
Saline	0.95 ± 0.20*	0.57 ± 0.09	0.76 ± 0.17
Low dose	0.85 ± 0.17	0.56 ± 0.08	0.87 ± 0.23
Medium	0.63 ± 0.11	0.50 ± 0.07	0.77 ± 0.16
High	0.59 ± 0.14	0.44 ± 0.08	0.81 ± 0.20

*Mean ± SEM.

TABLE 2

MEAN AFTERDISCHARGE DURATION (SECONDS) FOLLOWING COCAINE ADMINISTRATIONS

	Hippocampus	Amygdala	Septal region
Saline	96.9 ± 12.3*	77.7 ± 13.4	53.0 ± 14.6
Low dose	58.2 ± 5.2	52.0 ± 5.4	34.2 ± 10.6
Medium	42.2 ± 5.3	41.4 ± 3.3	24.5 ± 8.5
High	35.7 ± 4.4	31.5 ± 4.0	21.3 ± 6.4

*Means ± SEM.

Caudate stimulation failed to evoke AD in two of the three cats tested, even when high currents (up to 3 mA) and high frequencies (50–200 Hz) were applied during repeated stimulation sessions. In one subject, AD were evoked repeatedly with 50 Hz stimulation at two caudate sites. Thus, data on the effects of cocaine on caudate AD thresholds were limited. However, it is noteworthy that cocaine administrations resulted in consistent elevations of AD threshold for both of the caudate sites tested, rather than reductions. At one site, AD could not be evoked by currents up to 3 mA following six successive cocaine injections although AD were elicited regularly during each of the six alternate saline tests (mean AD threshold = 1.4 mA, 50 Hz). Testing the other caudate site following a 1 mg/kg dose resulted in a threshold 0.5 mA higher than the preceding saline test. AD were not elicited following five additional cocaine injections and again, AD were evoked during each of the alternating saline tests.

Stereotyped behaviors, which disrupted bar-pressing, occurred with each cocaine dose tested and were observed in all subjects.

Effects of Cocaine on Duration of Afterdischarges

In addition to alterations in AD threshold, substantial reductions in the duration of afterdischarges at all limbic sites regularly followed cocaine administration. The mean AD durations (in seconds) for each dose level are listed in Table 2. Similar reductions in AD duration were found for all limbic

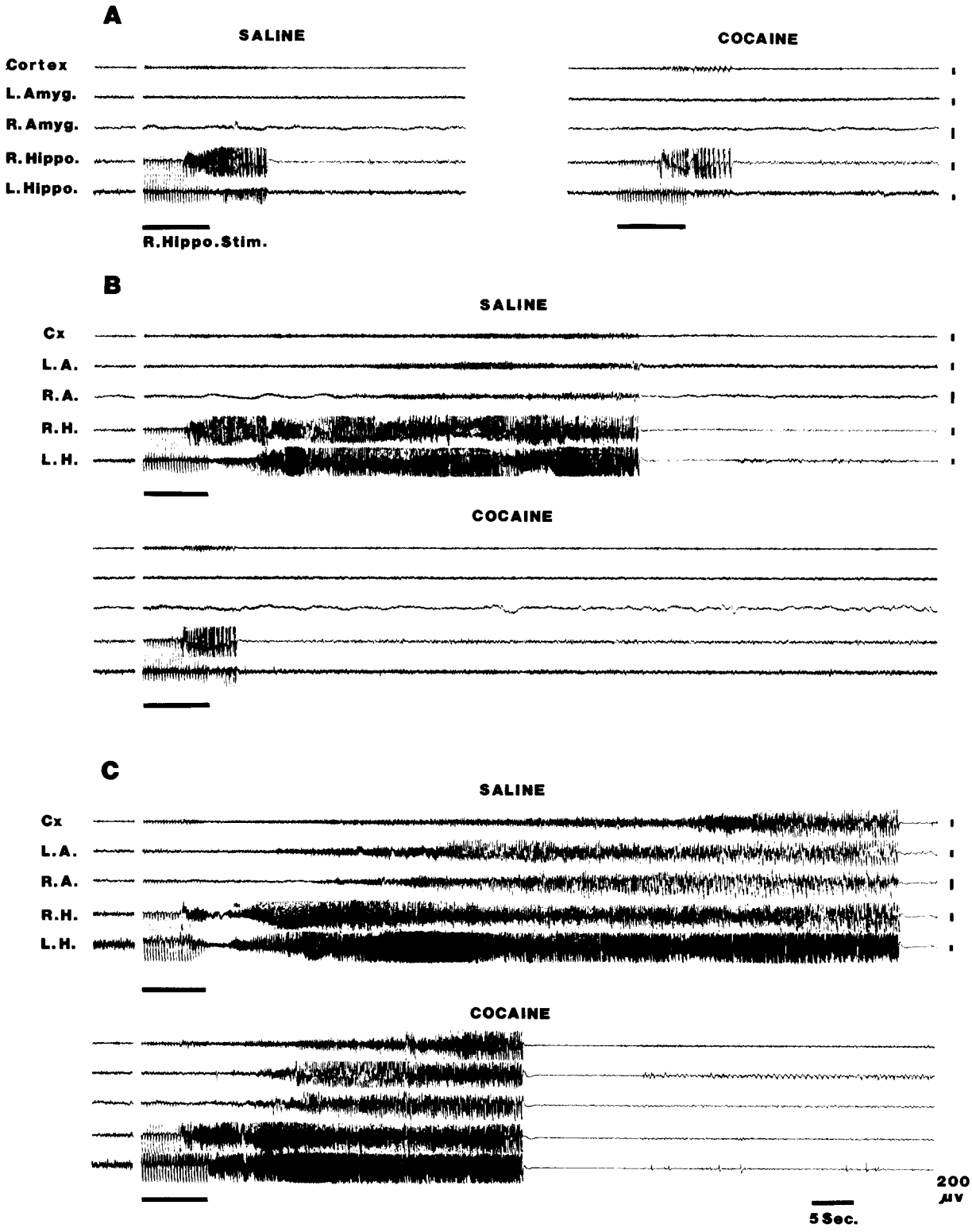

FIG. 1. Effects of alternate saline and cocaine administrations on afterdischarges evoked by right dorsal hippocampal stimulation during three stages of kindling. Note the reduction in AD duration following each cocaine administration. This effect occurred when the hippocampal AD was localized and there was no response to stimulation (A); when AD increased and the cat reacted with a brief head turning (B); and after propagation became diffuse and full motor seizures were evoked (C). In addition, propagation to the left hippocampus was initially blocked (A) and then substantially reduced (B) by cocaine.

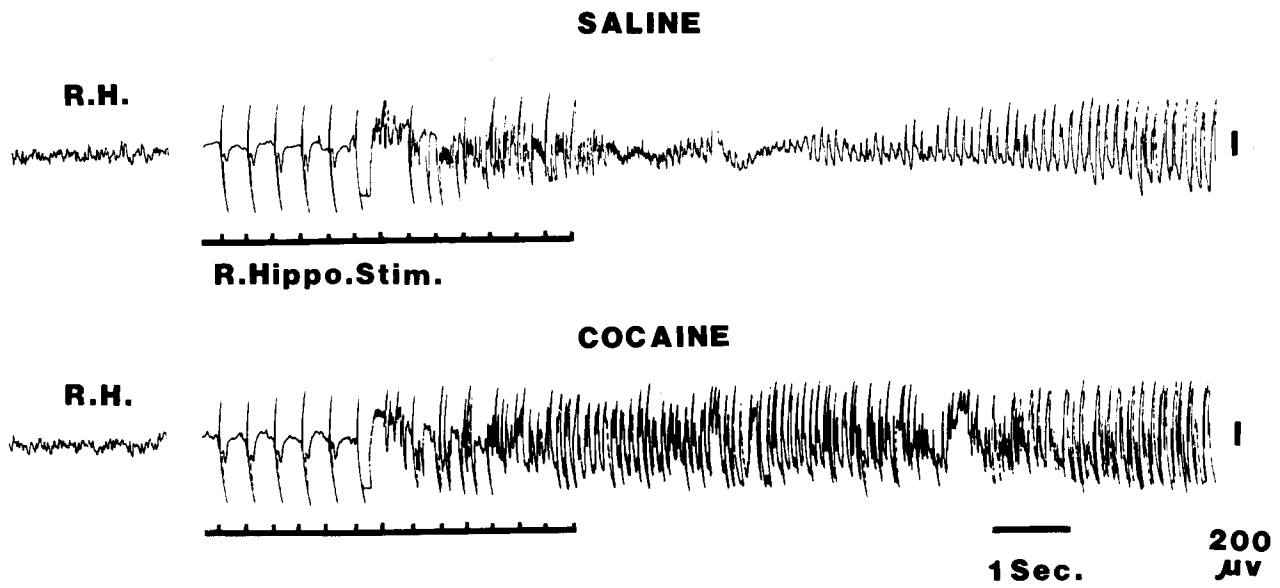

FIG. 2. Segments of tracings from right hippocampus in Fig. 1C, recorded at faster speed to show the initiation of afterdischarges during stimulation and the increased initial AD amplitude after cocaine administration.

sites—up to 63% in the hippocampus, 58% in the amygdala and 60% in the septal region. Analysis of variance indicated significant dose effects in the hippocampus, $F(3,18)=22.0$, $p<0.001$; the amygdala, $F(3,18)=7.5$, $p<0.002$; and the septal region, $F(3,6)=5.5$, $p<0.05$.

Effects of Repeated Drug Administrations

Analysis for drug-by-series interactions revealed neither potentiation nor diminution of responses during the four series of saline and cocaine administrations. The drug-induced changes in limbic AD thresholds were similar for the first and the second series of tests, $F(3,36)=2.6$, $p>0.05$. In subjects receiving an additional third and fourth test series, there were again no significant drug-by-series interactions, $F(9,27)=1.9$, $p>0.05$.

AD durations increased during the second series of tests, $F(1,12)=19.7$, $p<0.001$, as seizure development progressed and motor convulsions were often evoked by focal stimulation. The cocaine-induced decreases in AD duration were proportionately greater for the second test series while motor convulsions were developing, as indicated by the series-by-dose interaction, $F(3,36)=5.1$, $p<0.01$. In subjects receiving a third and fourth series of tests, motor convulsions were evoked consistently and there were no further changes in AD duration. The cocaine-induced reductions in duration remained unchanged.

Additional Electrophysiological Changes

Several additional electrophysiological effects were observed in association with the cocaine-induced alterations in afterdischarge duration and threshold. These changes included diminished propagation of discharges to distant limbic sites during early stages of seizure development, increased initial AD amplitude and a previously described reduction in propagation time [33].

These drug effects are illustrated in Figs. 1 and 2. Figure 1 displays a characteristic sequence of electrophysiological events as seizure development progressed during a series of limbic stimulation sessions. All recordings followed electrical stimulation of the right dorsal hippocampus at threshold intensity. The pairs of tracings (A, B and C) include responses to both a saline test and the alternate cocaine test (5 mg/kg) during three selected stages of seizure development. Afterdischarge durations during each cocaine test were reduced in comparison with each of the paired saline tests. This effect occurred first when epileptiform activity was localized to the hippocampus and there was no behavioral response (A) and in a later session (B) when interhemispheric propagation became prominent and the cat responded to stimulation with automatisms characteristic of focal limbic seizures (i.e., a brief controversive head turning and mouth movements). AD durations also declined subsequently after seizure discharges finally propagated diffusively to hippocampal, amygdalar and neocortical projections sites and fully developed motor convulsions were evoked (C). In addition, the time of onset of the projected discharges in the contralateral hippocampus, amygdala and cortex is seen to decrease following cocaine (C).

Transient reductions in the extent of propagation following cocaine administrations, observed in most subjects, are also illustrated in tracings A and B. Interhemispheric propagation to the left hippocampus, occurring regularly after saline injections, was first completely blocked (A) and then substantially reduced (B) following the alternate cocaine administrations. The brief hippocampal AD evoked during the 13th hippocampal stimulation session, following cocaine administration, (tracing B) reverts to a focal ictal pattern resembling the response after saline, at a much earlier stage of kindling (tracing A).

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 AD duration and AD threshold were conducted with a standard 30 mm/sec recording speed. Figure 2 illustrates brief segments of the right hippocampal afterdischarges of Fig. 1C, replayed at the faster recording speed. The initiation of the afterdischarge is evident while 3

Hz electrical stimulation is occurring. The AD amplitude reached a maximal level more rapidly following cocaine administration. The interval from onset of the afterdischarge to an amplitude exceeding 700 μV was 3 sec vs. 11 sec (Fig. 2). A reduction in this interval was observed consistently after cocaine administrations. For 11 paired tests with alternating 5 mg/kg cocaine and saline administrations, means were 2.4 sec (±0.4 SEM) vs. 6.8 (±1.4 SEM). These means were found to differ significantly ($p<0.01$; paired t-test).

Effects of Daily Cocaine Administration

Since no progressive changes in AD threshold occurred following the repeated, 96 hour drug administrations, we tested the possibility that sensitization or tolerance effects might develop during a series of daily cocaine treatments extending over a six-week period. However, no systematic changes in AD threshold were found during the series of cocaine and saline tests (2 conducted prior to the onset of daily drug administration and 12 tests at weekly intervals during the period of cocaine treatment). AD thresholds were reduced in all subjects following cocaine tests (21/21 tests). The mean threshold reduction for all tests was 0.161 mA (range 0.11–0.21 mA). The initial reduction occurring prior to the daily drug administrations, 0.163 mA (±0.017 SEM), was similar to the final threshold reduction after 6 weeks of chronic cocaine treatment, 0.176 mA (±0.012 SEM). There was no evidence of a progressive augmentation of the drug effect, $F(1,2)=5.8$, $p=0.14$ (trend analysis of the multivariate vector of mean differences).

AD durations increased during the series of cocaine and saline tests as focal afterdischarges gradually propagated to other limbic structures. AD durations were reduced following cocaine administrations (20/21 tests). The mean reduction in AD duration for all tests was 53.7%. The initial and final reductions were similar (53.7% vs. 54.8%) and there was no evidence of progressive changes, $F(1,2)=0.04$, $p=0.86$ (trend analysis of the multivariate vector of mean differences).

It should be noted that these experiments employed dorsal hippocampal stimulation which, in the cat, typically requires about 40 sessions to finally evoke full kindled seizures. Since only 14 electrical stimulation sessions were employed during the drug testing period, electrophysiological and behavioral responses were characteristic of early kindling stages (i.e., localized limbic afterdischarges and brief automatisms). Motor convulsions were never evoked by these electrical stimulations. It is also noteworthy that the repeated administrations of cocaine in 2.5 mg/kg and 5 mg/kg doses (61 injections per subject) never induced epileptiform discharges or motor seizures.

DISCUSSION

Relative Sensitivity of Limbic Structures to Electrical Stimulation

As indicated in Table 1, the amygdala and the hippocampus proved highly sensitive to low frequency stimulation. In order to evoke septal afterdischarges with similar current parameters, a threefold increase in stimulation frequency and coulomb threshold was required. These results are consistent with prior observations that the amygdala and hippocampus are brain structures with the highest susceptibility to epileptiform activity [1, 24, 26, 29, 48]. These previous studies, however, yielded conflicting results about the relative sensitivity of the two limbic structures. The present results suggest that a failure to control for the number of stimulations probably accounts for the discrepancies. Although initial AD thresholds for the hippocampus and the amygdala were almost identical, the amygdala proved significantly more sensitive after the threshold values stabilized following a series of baseline stimulations at each site.

The precipitous reduction in AD threshold during the first few stimulations, followed by rapid stabilization at a new level, is consistent with threshold changes observed for other responses to brain stimulation [10, 20, 54, 57]. Although afterdischarge thresholds stabilized rapidly, progressive kindling effects continued during a protracted series of stimulations, finally culminating in motor convulsions. These findings are at variance with early reports that kindling effects do not occur with 3 Hz limbic stimulation [21,22], but are consistent with other recent studies [6, 10, 32, 33]. The present results provide additional evidence that the kindling process is dependent upon repetitive induction of abnormal seizure afterdischarges and is not directly related to stimulus parameters employed or to the administration of repeated limbic stimulations *per se* [32,44]. Cocaine administrations did not prevent the evocation of diffuse seizure discharges and motor convulsions by 3 Hz stimulation (see Fig. 2C).

Effects of Cocaine on AD Thresholds

The present findings indicate that cocaine differentially affects the sensitivity of limbic structures to direct electrical stimulation. Larger dose-related AD threshold reductions were found following hippocampal stimulation and smaller, but significant, decreases occurred following amygdalar stimulation. There were no changes, however, in septal AD thresholds. In addition, significant increases in the initial AD amplitude followed cocaine administrations. These results suggest that subconvulsant doses of cocaine have differential excitatory effects on closely related limbic structures, increasing both the sensitivity of the hippocampus and amygdala to direct electrical stimulation and their propensity to respond with self-sustaining afterdischarges.

This effect may be an important factor responsible for the accelerated propagation of limbic seizure activity [33]. Excitability changes which enhance sensitivity to direct electrical stimulation, might also facilitate responses to repetitive discharges originating in distant, synaptically related brain sites. The present findings are consistent with previous reports that toxic doses of cocaine induce convulsions and generalized seizure patterns which begin in limbic structures [13, 14, 15]. The AD threshold lowering effect found in the present study also helps to account for the activation by cocaine of preexisting limbic seizure foci in patients with temporal lobe epilepsy [18]. In addition, the increased excitability, suggested by the present results, may contribute to the augmentation of 40/cps rhythmic activity of the amygdala observed following cocaine administration [13, 14, 15]. This fast rhythmic electrographic pattern is characteristically recorded in response to a variety of environmental stimuli which lead to emotional arousal [30, 31, 35].

Effects of Cocaine on AD Duration

Significant decreases in the duration of afterdischarges were found. There is a considerable contrast between drug effects on AD thresholds and AD duration. Substantial dose-related reductions in afterdischarge durations were

found at all limbic sites tested (including the septal region, where AD thresholds were unchanged). The magnitude of this drug response proved similar in the septal region, hippocampus and amygdala. Associated with reductions in AD duration, there were restrictions in the propagation of epileptiform activity to distant sites during early stages of seizure development. After motor convulsions developed, cocaine administration resulted in a compression of the entire ictal episode, including declines in AD duration at the structure stimulated, shorter propagated discharges and abbreviated motor convulsions. These findings suggest that cocaine has a widespread inhibitory action on neural mechanisms responsible for the maintenance and spread of self-sustaining epileptiform discharges.

Excitatory and Inhibitory Effects

Since convulsant and anticonvulsant properties of cocaine have been assigned to high or to low doses, it is noteworthy that the present study disclosed simultaneous excitatory and inhibitory neurophysiological effects. The same test doses decreased AD thresholds, and facilitated the spread of seizure patterns; but also reduced both AD duration and duration of propagated seizure discharges. These effects (which might be interpreted as both convulsant and anticonvulsant) increased over a wide range of doses, becoming maximal at the highest test dose which approached the convulsant threshold.

The seemingly paradoxical findings of a differential reduction of limbic AD thresholds, suggesting an excitatory effect, accompanied by a more widespread decrease in AD duration, suggesting an inhibitory effect, may be reconciled if cocaine affects independent neural mechanisms responsible for initiating and maintaining repetitive discharges. Many of the known actions of cocaine could lead to synaptic, or to nonsynaptically, generated changes in excitability which might facilitate the initiation of limbic afterdischarges and also abbreviate ictal events. These include direct actions on neuronal membranes interfering with transient increases in permeability to sodium and release of calcium [3,46], as well as the indirect actions of cocaine on various neurotransmitters, including dopamine [19], seratonin [38,47], norepinephrine [9] and acetylcholine [37].

Effects of Repeated Cocaine Administration

Neither potentiation nor attenuation of the cocaine-induced changes in limbic afterdischarge activity followed repetitive drug administrations. The absence of series-by-dose interactions during the repeated single-dose tests, as well as the absence of progressive responses during a six-week period of daily cocaine treatment indicate that neither tolerance nor sensitization effects developed. Moreover, limbic epileptiform discharges or convulsions were never induced by these repeated cocaine administrations. The present findings are consistent with behavioral studies reporting an absence of seizure sensitization after the chronic administration of moderate doses of cocaine [2, 17, 34]. They are at variance with other divergent reports of "reverse tolerance" effects involving very high doses [11, 40, 49, 52]. Since the later studies employed no electrophysiological recordings, it is difficult to separate drug sensitization from the non-specific effects of the limbic seizure discharges induced by toxic doses of cocaine.

The present findings carry implications for the interesting hypothesis that a type of "pharmacological kindling" is induced by cocaine which is analogous to the progressive electrophysiological effects observed after repeated limbic electrical stimulation [22]. It has been proposed that cocaine activates a progressive development and spread of abnormal limbic discharges and that similar synaptic mechanisms are responsible for both electrical kindling and abnormal behaviors following chronic cocaine treatment [16, 41, 43]. The present results suggest that cocaine has both inhibitory and excitatory actions on limbic seizure mechanisms, rather than a single activating effect. The pharmacological kindling paradigm, therefore predicts a series of cocaine-induced changes in evoked afterdischarges which differ from those found in the present experiments. Afterdischarge durations decreased, rather than increased following cocaine administration. The paroxysmal discharges were often restricted, rather than extended. Electrical ictal episodes and motor convulsions were attenuated. Although AD thresholds were reduced, this effect did not progress with repeated cocaine administrations. These complex electrophysiological responses occurred during both the early and late kindling stages.

The present findings help to account for recent failures to demonstrate a predicted increased rate of electrical kindling following chronic cocaine pretreatment [42, 45, 49] and suggest that the pharmacological kindling hypothesis may be untenable. However, electrical kindling effects and seizure sensitization following chronic cocaine administrations may share an important characteristic. If the electrical stimulus is well below threshold for AD, limbic stimulations can be repeated for years without kindling effects [32]. Similarly, if the dose of cocaine is substantially below the convulsant level, seizure sensitization effects do not occur after chronic administrations. The necessary condition for the progressive electrophysiological changes associated with seizure development, following either chronic cocaine treatment or repeated limbic electrical stimulations, may be the repetitive induction of localized epileptiform activity.

The present study provides evidence that cocaine, in subconvulsant doses, has potent but differential effects in modifying the excitability of closely related limbic structures. Concurrent excitatory and inhibitory effects on hippocampal, amygdalar and septal responsivity to direct electrical stimulation were suggested. These complex effects of cocaine are especially interesting since they involve limbic structures known to be of fundamental importance in the regulation of emotion, memory and information processing.

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