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Effect of Cocaine and Lidocaine on the Development of Kindled Seizures

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STRIPLING, J. S., C. A. GRAMLICH AND M. G. CUNNINGHAM. *Effect of cocaine and lidocaine on the development of kindled seizures*. PHARMACOL BIOCHEM BEHAV 32(2) 463–468, 1989.—The effect of a subconvulsive dose of cocaine or lidocaine on the development of kindling was studied in male Long-Evans rats. Animals were divided into three groups and kindled by daily electrical stimulation of the pyriform cortex. Fifteen minutes before each stimulation each animal received an intraperitoneal injection of either saline, 20 mg/kg cocaine hydrochloride, or 20 mg/kg lidocaine hydrochloride. Following kindling the drug treatment was discontinued and the transfer of kindling to a nondrug state was assessed by test stimulations given 2, 6, and 48 days after the last day of kindling. Both cocaine and lidocaine dramatically accelerated the development of kindling. Furthermore, the duration of clonus at kindling criterion was significantly longer in lidocaine-treated animals than in animals treated with saline, and the onset of clonus in cocaine-treated animals occurred significantly sooner after stimulation. However, this performance did not transfer fully to the nondrug state, with some animals failing to exhibit clonus. Among those animals exhibiting clonus at nondrug tests, afterdischarge duration was significantly higher in cocaine-treated than in saline-treated animals, but clonus duration was no longer elevated in lidocaine-treated animals, and the latency to clonus rose dramatically in animals previously treated with either cocaine or lidocaine. These results indicate that a subconvulsive dose of cocaine or lidocaine can facilitate the development of kindling when the drug is active at the time of electrical stimulation, apparently by means of the local anesthetic action shared by the two drugs. The kindling produced in this fashion is not entirely equivalent to kindling produced by electrical stimulation alone. In animals kindled under the influence of local anesthetics, the afterdischarge at the site of stimulation is expressed at least as strongly in the absence of the drugs as in their presence, but the spread of seizure activity to other areas of the brain, as reflected by the occurrence and latency of clonus, appears to have been temporarily enhanced by the drugs and is weakened in their absence.

Cocaine Lidocaine Kindling Pyriform cortex Rat

KINDLING is the progressive development of seizure activity due to repeated electrical stimulation of a specific brain site. It involves changes in seizure susceptibility at the site of stimulation and an enhanced propagation of the activity to other brain areas, culminating in a behavioral convulsion (1, 11, 12). Among the numerous drugs whose effects on kindling have been studied, cocaine is one of the most powerful. Cocaine has complex modulating effects on the expression of previously kindled seizures, including alterations in seizure threshold (7, 8, 21) and duration (6,15), and facilitation of seizure propagation and the onset of forelimb clonus (5, 15, 19). In addition, convulsions induced by cocaine facilitate subsequent limbic kindling (4,20) as well as certain aspects of neocortical kindling (22); repeated subconvulsive treatment with cocaine has no effect (18).

One aspect of cocaine's effects on kindling that has not yet been assessed is in some regards the most fundamental: what happens to the development of kindling when subconvulsive doses of cocaine are present in the brain at the time of each electrical stimulation? Racine, Livingston and Joaquin (14) have reported that procaine, which has local anesthetic effects like those of cocaine, facilitates kindling of the amygdala when given before each stimulation. The present experiment examined the effects of a subconvulsive dose of cocaine on the development of kindling, and compared its effects with those of lidocaine, a local anesthetic that lacks cocaine's monoaminergic properties. The kindling site was the pyriform cortex, a limbic structure that kindles rapidly (13), is strongly affected by local anesthetics (17), and may play a central role in all limbic kindling (9).

METHOD

Subjects

The subjects were male Long-Evans rats (Blue Spruce Farms) that weighed 280–350 g at surgery. They were housed individually in clear plastic cages, with food and water freely available. The colony room was maintained on a 12-hr/12-hr light/dark cycle, with all data collected during the light phase.

Surgery

Surgery was performed following the intraperitoneal administration of 42.5 mg/kg sodium pentobarbital, 100 mg/kg chloral hydrate, and 4 mg/kg atropine sulfate. The animal was placed in a stereotaxic instrument with the incisor bar positioned 5 mm above the plane of the ear bars, and a 200-μm diameter monopolar stainless-steel electrode was

implanted in the left pyriform cortex using the following coordinates: 2.4 mm anterior to bregma, 2.8 mm lateral at the dura, and 7.6 mm below the dura at a 14° lateral angle. A stainless-steel screw placed over the right frontal cortex served as a reference for stimulation and recording. A minimum of 18 days postoperative recovery was allowed before data collection began.

Procedure

Electrical stimulation throughout the experiment consisted of a 2-sec train of 0.2 msec cathodal square-wave pulses delivered to the pyriform cortex electrode at a frequency of 50 pulses/sec by a Grass S48 stimulator and PSIU6 stimulus isolation unit. The electrographic response to each stimulation was recorded using a Beckman R611 polygraph, and the behavioral response was monitored on closed-circuit television and recorded on videotape for subsequent analysis.

The design of the experiment is summarized in Table 1. On the first day of the experiment, each animal was tested for its afterdischarge threshold (ADT) to electrical stimulation of the pyriform cortex. The ADT was determined by repeated stimulation at 1-min intervals. Stimulation began at a current intensity of 10 μA and was increased in 10 μA increments until an afterdischarge (AD) was elicited. An AD was defined as a series of two or more electrographic spikes following stimulation. Animals not having an AD by 200 μA were excluded from the experiment. The ADT value obtained, referred to as ADT-1, was used as a basis for dividing the animals into three matched groups.

On the following day, a second ADT determination (ADT-2) was made. The procedure was the same as for ADT-1 except that no ceiling was placed on the ADT test current. Eight min before the first stimulation, animals in the three groups—designated SAL, COC, and LID—received intraperitoneal injections of physiological saline, 20 mg/kg cocaine hydrochloride (Merck), or 20 mg/kg lidocaine hydrochloride (Astra), respectively.

On the third day of the experiment, each animal was injected with the appropriate drug and 15 min later was stimulated with a single train of pulses with the current intensity set at 150% of the ADT-2 value. If no AD was triggered by the stimulation, the current intensity was increased in 50 μA steps and the animal stimulated at 1-min intervals until an AD was elicited. This procedure was repeated daily until the animal was kindled to a criterion of 2 consecutive ADs with clonus. In order to determine if the drug treatment influenced the expression of kindled seizures, the drug treatment and daily stimulation continued until each animal had exhibited 5 ADs with clonus. Only the first two ADs with clonus were used to measure the rate of kindling development in order to avoid the intrusion of inhibitory effects on seizure expression that can occur following repeated generalized seizures in the pyriform cortex and related areas [(2); Stripling and Russell, in preparation].

On the day following the last kindling stimulation, the drug treatments were administered for the last time and 8 min later the ADT was again determined (ADT-3). The following day the ADT was determined in the absence of drug treatment (ADT-4). To determine the persistence of kindling in the absence of the drugs, two more drug-free ADT determinations (ADT-5 and ADT-6) were made on the 6th and 48th day after the last kindling stimulation. At the end of the experiment electrode placement was verified histologically using the Prussian Blue technique (19).

TABLE 1

DESIGN OF THE EXPERIMENT AND SEIZURE GENERALIZATION OVER THE COURSE OF THE EXPERIMENT

Day	Electrical Stimulation	Drug Treatment	Proportion of Animals Exhibiting Clonus SAL (n=14)	COC (n=13)	LID (n=13)
1	ADT-1	No	0.00	0.00	0.00
2	ADT-2	Yes	0.00	0.62*†	0.08
3	Kindling	Yes	0.00	0.54*	0.54*
⋮	⋮	⋮	—	—	—
K	Kindling	Yes	1.00	1.00	1.00
K + 1	ADT-3	Yes	0.79	1.00	1.00
K + 2	ADT-4	No	0.79	0.77	0.77
K + 6	ADT-5	No	0.86	0.54‡	0.77
K + 48	ADT-6	No	1.00	0.92	1.00

K=number of days (1 AD per day) to 5th AD with clonus.
ADT=Afterdischarge threshold determination procedure.
Kindling=daily stimulation at 150% of ADT-2 current intensity.
Drug Treatment=saline, cocaine, or lidocaine administered before stimulation.
Specific comparisons using Fisher exact probability test ($p<0.05$, 2-tailed): *Significantly different from SAL group; †significantly different from LID group.
Specific comparisons using the binomial test ($p<0.05$, 2-tailed): ‡Significantly different from ADT-3.

Data Analysis

Fifty animals began the experiment. Seven failed to exhibit an AD at ADT-1 and were eliminated from the experiment, as were two others that exhibited clonus at ADT-1 (both had their stimulation electrode in the claustrum rather than the pyriform cortex). One animal died between ADT-5 and ADT-6, leaving 40 animals in the experiment. All had their stimulation electrodes in or on the border of the pyriform cortex.

Data were analyzed by analysis of variance followed by specific comparisons using the Newman-Keuls test. The Fisher exact probability test and the binomial test were used to analyze proportions (16).

RESULTS

As indicated in Table 2, there was a significant drug effect on kindling rate, $F(2,37)=17.33$, $p<0.001$, with both the COC and LID groups kindling significantly faster than the SAL group. The COC and LID groups did not differ significantly from each other in the number of ADs required to reach kindling criterion, but a significantly higher proportion of COC than LID animals had clonus at ADT-2 (the first AD triggered in the presence of the drug). This difference had disappeared by the next AD, when the majority of both COC and LID animals exhibited clonus (see Table 1). In contrast, no SAL animal exhibited clonus before the 5th AD.

Changes in ADT across the experiment are illustrated in Fig. 1. There was no significant group difference in ADT across the 6 tests, $F(2,37)=0.83$, but there was a significant decline over time, $F(5,185)=25.45$, $p<0.001$, and a significant Group × Time interaction, $F(10,185)=3.46$, $p<0.001$.

TABLE 2

EFFECT OF DRUG TREATMENT ON KINDLING RATE (MEAN ± S.E.M.)

Group	N	ADs to Criterion (2 consecutive ADs with clonus)
SAL	14	9.1 ± 0.9
COC	13	4.2 ± 0.3*
LID	13	5.5 ± 0.5*

*Significantly different from the SAL group (Newman-Keuls test, $p<0.05$).

Specific comparisons indicated that cocaine significantly elevated threshold at ADT-2 (in the presence of the drug), and that LID animals had a significantly higher threshold at ADT-6 than SAL animals (in the absence of the drug). No other comparisons were significant.

When ADT is determined by the stairstep method used here, there is a tendency for the pyriform cortex to respond with a single spike at a lower current intensity than that required to trigger a sustained AD. This tendency appears specific to the pyriform cortex, as we have not seen it with stimulation of the olfactory bulb or amygdala [e.g., (2)]. In the present experiment this tendency was small in SAL animals (1 of 14 at ADT-2) but increased significantly in COC animals (9 of 13; $p<0.05$, Fisher exact probability test) and to a lesser extent in LID animals (5 of 13). Consequently, the threshold for a single electrographic spike was also analyzed (see Fig. 1). As with ADT there was a significant decline over time, $F(5,185)=18.95$, $p<0.001$, and no significant group effect, $F(2,37)=0.46$; however in this case there was also no significant Group × Time interaction, $F(10,185)=0.72$. Specific comparisons indicated that LID animals still had an elevated threshold at ADT-6, but the cocaine-induced increase in ADT-2 was eliminated. This suggests that the cocaine-induced elevation of ADT seen in Fig. 1 was due to an enhanced ability to terminate seizure activity in the pyriform cortex after a single spike rather than to a complete suppression of all seizure activity at lower currents. Regardless of which measure of threshold is used, the reduction in threshold seen after kindling in the drug groups transferred fully from a drug state (ADT-3) to a nondrug state (ADT-4).

Because the two drug groups had a higher ADT-2 threshold, which in turn determined the current intensity used during kindling, the possibility must be addressed that the differences in kindling rate seen in this experiment were due to differences in kindling current. If this interpretation were correct there should be a negative correlation between the ADT-2 current intensity and the number of ADs to kindling criterion. However, the actual correlation (pooled Pearson product-moment correlation coefficient) does not support this possibility, $r(38)=0.08$. Furthermore, we have found no effect of current intensity on pyriform cortex kindling in a separate experiment designed to address this issue (Stripling and Russell, in preparation). It therefore appears that the drug effect on kindling rate seen here cannot be attributed to the stimulation intensity used.

Seizure generalization across the 6 ADT tests, as measured by the occurrence of clonus, is presented in Table 1.

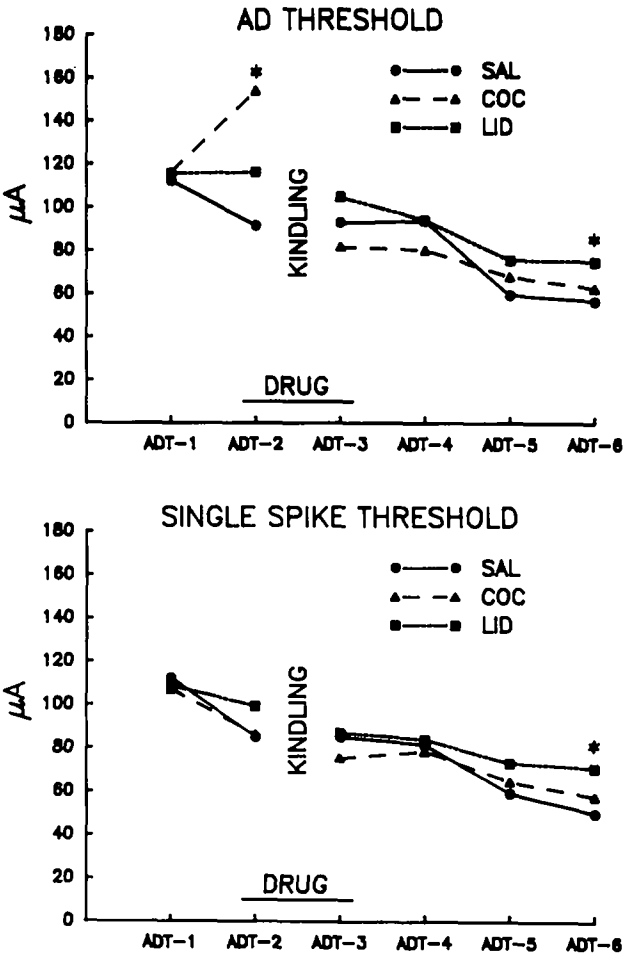

FIG. 1. Mean current intensity thresholds for an AD (a series of 2 or more spikes) or for a single spike at the 6 AD threshold tests. Drugs were administered before stimulation at ADT-2, during kindling, and at ADT-3. Note that the interval between successive ADT determinations was not constant (see Table 1). Groups: SAL=physiological saline (n=14); COC=cocaine (n=13); LID=lidocaine (n=13). Specific comparisons between groups using Newman-Keuls test ($p<0.05$): *significantly different from SAL.

Unlike the reduction in ADT, seizure generalization in the two drug groups did not transfer completely from a drug state (ADT-3) to a nondrug state (ADT-4 and ADT-5). The interpretation of this outcome is clouded by the absence of clonus in some SAL animals as well.

The expression of generalized seizures in the presence and absence of the drugs was assessed by comparing seizure expression on the first 5 days with clonus during kindling and at ADT-3, ADT-4, and ADT-6. For this analysis a seizure was considered to be generalized when it produced bilateral forelimb clonus. This permitted each AD to be divided into three components: clonus latency (the time required for the seizure to generalize), clonus duration (the generalized component of the seizure), and AD after clonus (persistence of the seizure at the recording site after generalization ceases). Only animals exhibiting generalized seizures on each day of the analysis (n=31) were included. Because of the low incidence of generalized seizures in the COC group at ADT-5 (see Table 1), data from ADT-5 were excluded from the analysis.

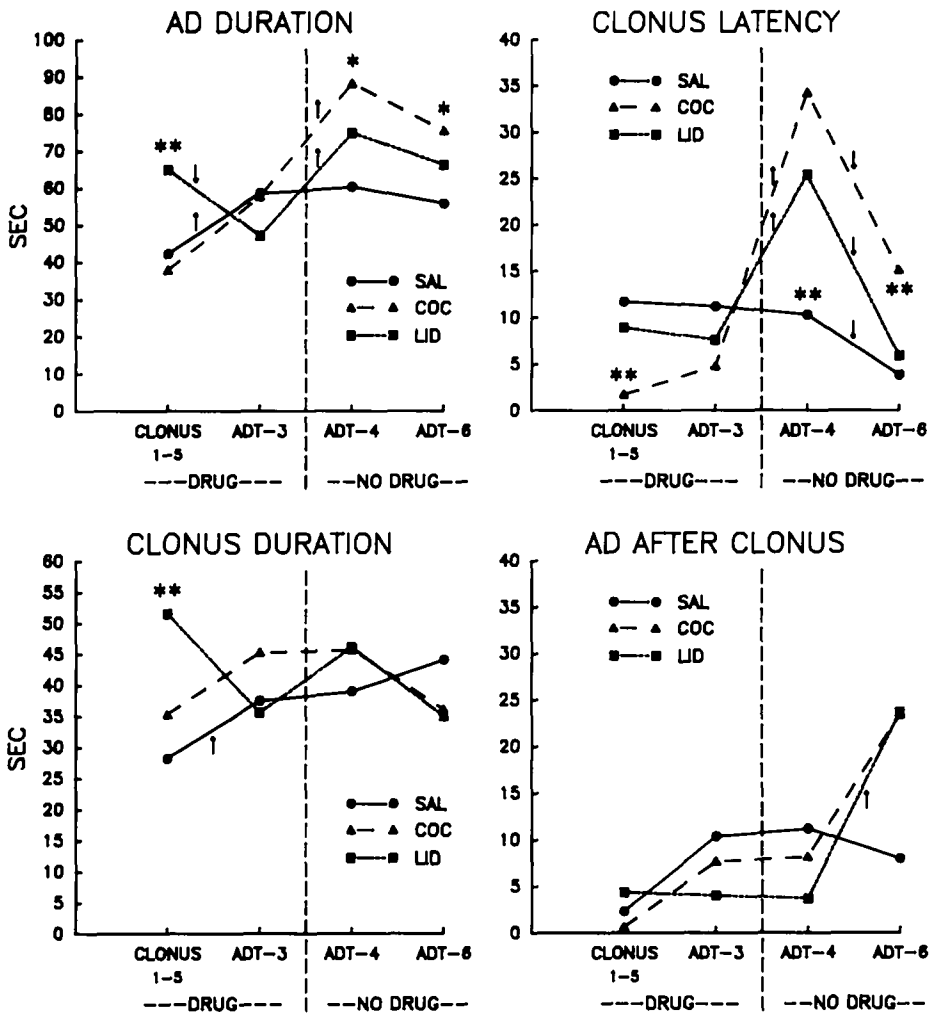

FIG. 2. Expression of generalized seizures across the course of the experiment. The vertical dashed line divides seizures elicited in the presence of the drugs from seizures elicited in their absence. Clonus 1–5 represents the mean response across the first 5 days with clonus during kindling. Only animals that exhibited a generalized seizure at each point in the figure were included in this analysis; data from ADT-5 were not included because of the low incidence of generalized seizures on that day. Groups: SAL=physiological saline (n=11); COC=cocaine (n=10); LID=lidocaine (n=10). Specific comparisons between groups using Newman-Keuls test ($p<0.05$): *significantly different from SAL; **significantly different from both other groups. Significant changes within a group over time (Newman-Keuls test, $p<0.05$) are indicated by an arrow located between the two points in time; the direction of the arrow indicates an increase (up) or decrease (down).

The results of the analysis are shown in Fig. 2. An initial series of 2-factor ANOVAs revealed no significant group effects (largest $F=1.59$), but a significant change over time for AD duration, $F(3,84)=12.84$, $p<0.001$, clonus latency, $F(3,84)=18.01$, $p<0.001$, and AD after clonus, $F(3,84)=6.84$, $p<0.001$, as well as a significant Group × Time interaction for AD duration, $F(6,84)=4.44$, $p<0.001$, clonus latency, $F(6,84)=7.12$, $p<0.001$, and clonus duration, $F(6,84)=3.28$, $p<0.01$. Specific comparisons were conducted using 1-factor ANOVAs for each time point or group followed by the Newman-Keuls test; these comparisons form the basis for the description which follows.

During the first 5 ADs with clonus (Clonus 1–5), both lidocaine and cocaine enhanced seizure generalization, but with different patterns. Lidocaine significantly increased clonus duration, resulting in a significantly increased AD duration as well. Cocaine did not significantly increase clonus duration in comparison to saline, but it dramatically decreased clonus latency, producing seizure generalization almost immediately after stimulation. An examination of Fig. 2 reveals that at this point in the study seizures in COC animals were generalized for almost their entire duration (i.e., clonus latency and AD after clonus were near zero).

At ADT-3 there were no significant differences among the groups in AD duration or any seizure component. SAL animals exhibited a significant increase in clonus duration from Clonus 1–5 to ADT-3, with a consequent increase in AD duration. A similar increase in COC animals did not

reach significance. These changes were due primarily to an increase in clonus duration across the first few generalized ADs in kindling. In marked contrast to the other two groups, LID animals exhibited a significant decline in AD duration and a similar but nonsignificant decline in clonus duration. Because lidocaine was present at both times, this change appears due to the difference in stimulation procedure (a single supra-threshold stimulation per day during Clonus 1–5 vs. the AD threshold determination procedure at ADT-3).

A comparison between ADT-3 (in the presence of the drug) and ADT-4 (in the absence of the drug) permits an evaluation of the effect of the drug itself on seizure expression. There was a significant and dramatic increase in clonus latency from ADT-3 to ADT-4 in both COC and LID animals, accompanied by a significant increase in AD duration. At ADT-4, clonus latency was significantly longer for COC and LID animals than for SAL animals, and AD duration was significantly longer for COC animals. Clonus duration and AD after clonus remained unchanged in all groups.

ADT-6, conducted 47 days after the last drug administration and 42 days after the last previous AD (see Table 1), provides a measure of the persistence of kindling in the three groups. All three groups declined significantly in clonus latency from ADT-4 to ADT-6, with COC but not LID animals remaining significantly elevated above SAL animals. As a consequence, AD duration was also significantly elevated for COC but not LID animals in comparison to SAL animals. AD after clonus increased from ADT-4 to ADT-6 in both COC and LID animals, but this increase reached significance only in LID animals. Both drug groups declined in clonus duration, but this change did not reach significance in either group.

Overall, the data in Fig. 2 and Table 1 can be summarized as follows. At kindling criterion, seizure generalization, as reflected by reduced clonus latency or elevated clonus duration, was enhanced in COC and LID animals. When the drugs were withdrawn (after ADT-3) there was an increase in AD duration in COC and LID animals due to an increase in the duration of the nongeneralized portions of the seizure (clonus latency and/or AD after clonus). Clonus duration itself remained relatively stable. The dramatic rise in clonus latency at this point and the decline in the proportion of animals with clonus (see Table 1) indicate that seizure generalization had been temporarily enhanced by the presence of the drug. It should be noted that among those COC and LID animals that exhibited clonus at all test points in Fig. 2, clonus duration in the nondrug state was comparable to that of SAL animals; the aspects of seizure expression that did not transfer well to the nondrug state were those temporarily enhanced beyond the performance of SAL animals by the drugs (i.e., reduced clonus latency in COC animals and elevated clonus duration in LID animals).

DISCUSSION

In this experiment both cocaine and lidocaine strongly facilitated the development of kindled seizures when given daily prior to kindling stimulation. This effect was particularly prominent in cocaine-treated animals, the majority of which exhibited clonus the first time an AD was elicited in the presence of the drug (ADT-2). Expression of the electrographic seizure at the site of stimulation transferred fully to the nondrug state, but the spread of seizure activity to other areas of the brain, as reflected by the occurrence and latency of clonus, appears to have been temporarily enhanced by the drugs and was reduced somewhat in their absence. These results are consistent with those of Racine *et al.* (14), who found that procaine facilitated amygdala kindling, but that seizure generalization was diminished following stimulation in the absence of the drug.

Part of the explanation for cocaine's effects on kindling development may lie in its previously documented influences on seizure expression. Cocaine facilitates the propagation of seizure activity triggered by electrical stimulation from the site of stimulation to other sites in the brain (5). In previously kindled animals this effect is expressed behaviorally by more rapid onset of the generalized seizure: a dramatic reduction in clonus latency following stimulation of the olfactory bulb (19) or pyriform cortex [(15,19); the present study], or more rapid replacement of the focal tonic seizure in neocortical kindling with a generalized motor seizure (22). Lidocaine has similar effects (15, 19, 22). These effects are transitory and are seen only in the presence of the drug. By facilitating seizure propagation, cocaine, given before each kindling stimulation as in the present experiment, may act to transform focal or anatomically-restricted seizures occurring early in the kindling process into generalized seizures (i.e., seizures accompanied by forelimb clonus), causing an apparent facilitation of the kindling process. These drug-enhanced seizures would contribute to the kindling process, but because animals treated with cocaine reach kindling criterion very quickly, their cumulative "dose" of seizure activity across days is less than in control animals that kindle at the normal rate. Consequently, they may not be as fully kindled as controls and when tested in the absence of the drug may be more prone to revert to a nongeneralized seizure or to exhibit an elevated clonus latency.

Although seizure generalization did not transfer fully to the nondrug state in animals kindled under the influence of cocaine or lidocaine, the expression of the electrographic seizure and the reduction in AD threshold showed complete transfer. There is evidence that cocaine and other local anesthetics act selectively upon the forebrain (3), and specifically the olfactory forebrain (17), in a manner distinct from other convulsant drugs such as pentylenetetrazol (2,3). Thus, these drugs may have selectively facilitated those aspects of the kindling process, such as AD threshold and the electrographic seizure, which are likely due to functional changes at or near the site of stimulation. Previous research has shown that convulsions induced by cocaine facilitate subsequent kindling of the olfactory bulb (20); in that study the electrographic seizure was elevated in duration at kindling criterion and remained so over a 3-week period, while the behavioral component declined significantly. The same treatment facilitates the development of the electrographic but not the motor seizure in subsequent cortical kindling (22). In the present experiment the administration of cocaine before each kindling stimulation may have channeled the electrically triggered seizure into a pattern resembling a cocaine-induced seizure, producing an effect similar to those described above.

Cocaine and lidocaine were similarly effective in facilitating the development of kindling in the present experiment, a finding consistent with the hypothesis that cocaine acted to facilitate kindling development by means of its local anesthetic action. There were two differences in the characteristics of the resulting seizures that merit discussion. First, lidocaine resulted in longer generalized seizures during kindling than did cocaine. This difference has also been demonstrated in the expression of previously kindled sei-

zures in the pyriform cortex and may be due to cocaine's monoaminergic effects (15). It is not likely to be due to any difference in their potency as local anesthetics, as previous research in our laboratory has indicated that cocaine and lidocaine are roughly equivalent in their ability to produce local anesthetic effects on olfactory spindle activity and evoked potentials (10,17). The second difference is the failure of lidocaine to reduce clonus latency during kindling (see Fig. 2). This result is striking, because lidocaine has strongly reduced clonus latency in previous experiments when given just before a generalized seizure is triggered in a previously-kindled animal (15,19). A possible explanation is that the repeated occurrence of long generalized seizures in the lidocaine group resulted in a substantial build-up of inhibitory processes that oppose the expression of subsequent seizures. Our laboratory has documented that daily generalized seizures in the pyriform cortex can have this effect (Stripling and Russell, in preparation). This interpretation is supported by evidence linking the occurrence of long generalized ADs to subsequent inhibition of seizure generalization in amygdala kindling and to a rise in clonus latency in olfactory bulb kindling (2).

Previous research in our laboratory has demonstrated both pro- and anticonvulsant effects of cocaine and related drugs on the development of kindling and the expression of kindled seizures. Both cocaine and lidocaine can elevate AD threshold (21,22), thereby opposing seizure expression. However, once AD threshold is exceeded, cocaine and lidocaine facilitate generalization of the resulting seizure (15, 19, 22). The drug effects observed in the present experiment appear to be the result, either direct or indirect, of a transitory increase in seizure generalization due to the presence of cocaine or lidocaine at the time of kindling stimulation. These seizures, although only temporarily enhanced by the drug, nonetheless produced an enduring facilitation of at least one aspect of the kindling process, the development of the afterdischarge at the site of stimulation.

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