*Pharmacology Biochemistry & Behavior*, Vol. 15, pp. 793–798, 1981. Printed in the U.S.A.

# Facilitation of Kindling by Convulsions Induced by Cocaine or Lidocaine but not Pentylenetetrazol[1]

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Received 6 July 1981

STRIPLING, J. S. AND C. HENDRICKS. *Facilitation of kindling by convulsions induced by cocaine or lidocaine but not pentylenetetrazol.* PHARMAC. BIOCHEM. BEHAV. 15(5) 793–798, 1981.—The effect of drug-induced convulsions on kindling was studied in male Long-Evans rats. In Experiment 1 rats experienced a single convulsion induced by the intravenous infusion of cocaine, lidocaine, or pentylenetetrazol (PTZ), or received a control infusion of saline. Beginning eight days later all animals were kindled by daily stimulation of the olfactory bulb. Animals which had been convulsed by cocaine or lidocaine kindled significantly faster than either saline controls or PTZ-convulsed animals, which did not differ significantly. Experiment 2 was conducted to determine if an effect of PTZ on kindling could be obtained with repeated convulsions. Rats experienced three convulsions induced by cocaine or PTZ at 72 hr intervals, or control infusions of saline. Kindling began on the eighth day after the last infusion. Cocaine-convulsed animals again kindled significantly faster than saline or PTZ-convulsed animals, which did not differ significantly. The cocaine animals also had significantly longer afterdischarges than the saline group at the end of kindling and when stimulated again 21 days after kindling was completed. These results suggest that the facilitating effect of cocaine-induced convulsions is not a general property of all convulsants but is a more specific effect which is apparently shared by other local anesthetics.

Cocaine Lidocaine Pentylenetetrazol Kindling Olfactory bulb Convulsion Rat

IN high doses cocaine produces a characteristic form of clonic convulsion [7]. This effect appears to be primarily of local anesthetic origin, since other local anesthetics such as lidocaine produce similar convulsions [26,37]. Several studies have reported that the production of one or more convulsions by cocaine can increase the subsequent convulsant effect of the drug [6, 27, 33, 35], although other studies have reported tolerance [5, 21, 22]. While this conflict concerning sensitization vs tolerance with cocaine has yet to be resolved, a similar form of sensitization has been reported for other convulsant drugs such as lidocaine [26], pentylenetetrazol [2, 14, 19, 23, 24], flurothyl [1,28], and cholinergic agents [9,36], as well as for other methods of producing a convulsion such as electroconvulsive shock [32]. In addition, there is evidence of cross-sensitization between convulsant agents, in which repeated administration of one agent results in sensitization to another [1, 20, 25].

A related phenomenon is that of kindling, in which repetition of electrical brain stimulation which initially produces only a localized electrophysiological seizure results in a gradual sensitization so that eventually the electrical stimulation triggers widespread electrophysiological seizure activity accompanied by a behavioral convulsion [12,30]. There is some evidence of cross-sensitization between kindling and convulsant drugs [4, 10, 11, 25]. Recently Kilbey, Ellinwood and Easler [16] reported that rats which had experienced one to three convulsions induced by cocaine kindled significantly faster than controls in response to stimulation of the amygdala. The purpose of the experiments reported here was to determine whether this effect is a general property of convulsant drugs or is related to a specific pharmacological action of cocaine.

## EXPERIMENT 1

Experiment 1 was designed to determine whether kindling is facilitated by a single convulsion induced by cocaine, lidocaine, or pentylenetetrazol (PTZ). Lidocaine is a local anesthetic which produces convulsions similar to cocaine's, while PTZ-induced convulsions have a behavioral profile distinctly different from those produced by cocaine or lidocaine. The olfactory bulb (OB) was chosen as the site of kindling because cocaine and lidocaine, in doses approaching the convulsive threshold, produce pronounced electrophysiological activity ("local anesthetic spindles") in the OB and its major projection site, the prepyriform cortex (Stripling, manuscript in preparation).

### METHOD

*Subjects*

The subjects were 34 male Long-Evans rats (Blue Spruce

[1]This research was supported by a grant from the University Research Council of the University of Arkansas. Address reprint requests to J. S. Stripling.

Farms) which weighed 295–390 g at the time of surgery. They were housed individually in clear plastic cages and were maintained on a 12 hr/12 hr light/dark cycle with food and water freely available throughout the experiment. All testing occurred between the second and eighth hour of the daily light period.

*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. With the incisor bar positioned 5 mm above the plane of the ear bars, each animal was stereotaxically implanted with a monopolar electrode (200 $\mu$m diameter enamel-insulated stainless steel wire) in the granule cell layer of the left OB (9.1 mm anterior to bregma, 1.2 mm lateral, and 1.5 mm below the dura). (An electrode was also implanted in the left caudate nucleus, but the data from that electrode provided no additional information and will not be reported here.) Stainless steel screws placed over the right anterior cortex and left posterior cortex served as references for stimulation and recording, respectively. Each animal was also implanted with a Silastic catheter (0.635 mm o.d.) in the right external jugular vein. The animals were allowed a minimum of 15 days post-operative recovery before the experiment began.

*Apparatus*

During data collection the animal's home cage was placed in a clear acrylic recording chamber enclosed within a larger chamber for visual and acoustic isolation. The cable used for stimulation and recording was mounted on a BRS/LVE slip-ring commutator attached to a counterbalanced arm, allowing the animal full freedom of movement. The animal's behavior was monitored via closed circuit TV and recorded on video tape for subsequent analysis. A Grass S48 square-wave stimulator and PSIU6 stimulus isolation unit were used for stimulation and a Beckman R611 polygraph for recording. Intravenous infusions were made through a fluid channel in the slip-ring commutator using a Harvard 975 infusion pump.

*Procedure*

The basic experimental design was as follows. The animals were divided into four groups: a control group which received saline and three experimental groups which experienced a convulsion induced by either cocaine, lidocaine, or PTZ. Following an eight-day waiting period to allow any transitory effects of the convulsion to dissipate, all animals were kindled to criterion by daily electrical stimulation of the olfactory bulb.

The drug-induced convulsions were produced by slow intravenous infusion. Animals received either cocaine hydrochloride (20 mg/ml), lidocaine hydrochloride (20 mg/ml), or PTZ (40 mg/ml) infused at a rate of 0.25 ml/min. Each infusion was continued until the onset of electrophysiological seizure activity and behavioral convulsions. Control animals received an infusion of physiological saline whose duration was the mean of the other three groups.

The intensity of the clonus produced by the convulsant drugs was measured by a 4-point rating scale: (1) mild; (2) moderate; (3) vigorous; (4) severe. In order to obtain a substantial convulsant effect with PTZ, infusions were continued beyond the onset of myoclonic jerks until sustained clonus occurred. These clonic convulsions often became generalized and were frequently accompanied by loss of equilibrium. Lidocaine produced ataxia and immobility, and animals tended to receive very high doses before convulsing, resulting in prolonged seizures with substantial risk of death. To avoid this problem lidocaine animals were briefly picked up at 90 sec into the infusion and at 30 sec intervals thereafter until they convulsed. Picking the animal up in this fashion tended to trigger the convulsion and thereby reduce its duration and potentially lethal effects.

Kindling began on the eighth day following the intravenous infusion. During kindling the OB was stimulated by a 2-sec train of monopolar negative square wave pulses of 0.2 msec duration at a rate of 50 pulses/sec. On the first day of kindling the afterdischarge (AD) threshold of the OB was determined as follows. Each animal was initially stimulated at a current level of 50 $\mu$A. At 60 sec intervals the current level was increased 50 $\mu$A and the stimulation repeated until an AD was evoked in the OB. Animals not exhibiting an AD by 800 $\mu$A were discarded from the experiment. On all subsequent days of kindling an AD was elicited in each animal by stimulation at its AD threshold as determined on the first day. The behavioral response to kindling was measured in four stages: (1) chewing movements; (2) forelimb clonus; (3) forelimb clonus and rearing to a fully vertical position; (4) forelimb clonus, rearing, and falling. Each animal was stimulated daily until a stage 3 or 4 response occurred on two consecutive days, or until a maximum of 18 days of stimulation was reached. Animals which did not exhibit a stage 2 response (clonus) within 18 days of stimulation were discarded from the experiment. Animals which did exhibit a stage 2 response but did not reach the kindling criterion were retained in the experiment and given the maximum score for AD's to criterion. At the end of the experiment electrode positions were verified histologically using the Prussian blue technique as described elsewhere [34].

*Data Analysis*

Of the 34 animals which began the experiment, one cocaine animal died during a convulsion, one lidocaine animal was discarded due to a faulty catheter, and one PTZ animal was discarded for failure to exhibit clonus within 18 days. This left 7 animals in the PTZ group and 8 each in the saline, cocaine, and lidocaine groups. The data for these animals were analyzed by analysis of variance followed by specific comparisons using Tukey's (a) test [38].

## RESULTS

Information concerning the convulsion induced by the various drugs is presented in Table 1. There was a significant difference among the groups in the duration of the clonic convulsions (and electrophysiological seizure activity) induced by the drugs, $F(2,20)=5.75$, $p<0.05$, with lidocaine producing significantly longer seizure duration than cocaine. There was also a significant difference in the rated intensity of the clonus, $F(2,20)=16.35$, $p<0.001$, with lidocaine producing significantly weaker clonus. The convulsions induced by the three drugs had no significant effect on weight gain between the convulsion and the first day of kindling, $F(3,26)=1.09$.

The response of the groups to kindling is presented in Table 2. There was no significant difference among the groups in the AD threshold of the OB on the first day of kindling, $F(3,27)=1.42$. However, the drug-induced convul-

TABLE 1

CHARACTERISTICS OF THE DRUG-INDUCED CONVULSION IN EXPERIMENT 1 (MEANS ± S.E.M.)

| Group | N | Dose Administered (mg/kg) | Clonus Duration (sec)* | Clonus Intensity (rating) |
|---|---|---|---|---|
| Cocaine | 8 | 9.1 ± 0.4 | 20.5 ± 4.9‡ | 1.9 ± 0.1‡ |
| Lidocaine | 8 | 27.7 ± 3.2 | 43.4 ± 4.1 | 1.1 ± 0.1 |
| PTZ | 7 | 17.8 ± 0.8† | 28.0 ± 5.9 | 2.1 ± 0.1‡ |

*Total clonus duration summed across one or more episodes.

†Mean dose for 5 animals in the PTZ group which received an intravenous infusion. The remaining 2 animals had faulty catheters and received a subcutaneous rather than intravenous infusion. They convulsed at a dose of 75.7 ± 9.2 mg/kg.

Specific comparisons using Tukey's (a) test: ‡significantly different from lidocaine group at 0.05 level.

sions had a highly significant effect on the rate of kindling, as measured by the number of AD's required to produce two consecutive stage 2 responses (forelimb clonus), $F(3,27)=7.99$, $p<0.001$. A convulsion induced by cocaine or lidocaine significantly facilitated kindling, while a PTZ-induced convulsion did not. When kindling was measured to a stricter criterion of two consecutive stage 3 or 4 responses (rearing or falling), there was again a highly significant effect, $F(3,27)=5.14$, $p<0.01$, but only the cocaine group kindled significantly faster than the saline group.

In order to determine whether animals in the four groups were responding similarly to the stimulation at the time kindling was completed, various measures of each animal's performance on its last day of kindling were analyzed. There was no significant difference among the groups in AD duration or amplitude, in the stage of kindling exhibited, or in the latency or duration of the clonus produced (largest F value $=1.53$).

## EXPERIMENT 2

Experiment 1 indicated that a single convulsion by cocaine or lidocaine produces a significant facilitation of kindling of the olfactory bulb while a convulsion induced by PTZ is ineffective. Although the convulsions induced by PTZ appeared comparable in duration and behavioral intensity to those produced by the other drugs (see Table 1), it is possible that in some way the convulsions produced by the three drugs were not well matched, and that a more extensive PTZ treatment would also have facilitated kindling. The purpose of Experiment 2 was to explore this possibility by producing three drug-induced convulsions rather than one.

### METHOD

*Subjects*

The subjects were 31 male Long-Evans rats (Blue Spruce Farms) which weighed 310–400 g at the time of surgery. They were housed as in Experiment 1. All testing occurred between the third and ninth hour of the daily light period.

*Procedure*

Animals were implanted with a monopolar electrode in the left OB, a single cortical screw for use as a reference during stimulation and recording, and an intravenous catheter as described in Experiment 1. A minimum of 15 days post-operative recovery was allowed before the experiment began.

The apparatus and general experimental procedure were unchanged from Experiment 1. The animals were divided into three groups. Animals in the cocaine and PTZ groups experienced three convulsions at 72 hr intervals produced by intravenous infusion of the appropriate drug. Animals in the saline group received three infusions of physiological saline. Kindling began on the eighth day following the last infusion. Animals were kindled to criterion as in Experiment 1. On the 21st day after reaching kindling criterion, each animal was again stimulated to assess the permanence of the kindling produced. At the end of the experiment electrode placements were histologically verified.

Of the 31 animals which began the experiment, one cocaine and one PTZ animal died during the drug-induced convulsions. One cocaine animal was discarded when it failed to exhibit an AD on the first day of kindling (histology later revealed its electrode to be in the external plexiform layer rather than the granule cell layer of the OB), and one saline animal was discarded for failure to exhibit clonus within 18 days of kindling. This left 8 saline, 9 cocaine, and 10 PTZ animals in the experiment.

TABLE 2

EFFECT OF DRUG TREATMENT ON KINDLING IN EXPERIMENT 1 (MEANS ± S.E.M.)

| Group | N | AD Threshold (μA) | AD's to Criterion | | AD Duration on Last Day of Kindling (sec) |
|---|---|---|---|---|---|
| | | | Stage 2 | Stages 3–4 | |
| Saline | 8 | 319 ± 63 | 9.1 ± 0.9 | 10.3 ± 0.9 | 60.4 ± 5.8 |
| Cocaine | 8 | 375 ± 57 | 5.4 ± 0.5*† | 6.0 ± 0.6* | 77.0 ± 7.5 |
| Lidocaine | 8 | 463 ± 68 | 5.1 ± 0.5*† | 7.1 ± 1.1 | 75.9 ± 9.4 |
| PTZ | 7 | 493 ± 78 | 8.3 ± 0.9 | 9.1 ± 0.7 | 82.0 ± 6.8 |

Specific comparisons using Tukey's (a) test: *significantly different from saline group at 0.05 level; †significantly different from PTZ group at 0.05 level.

TABLE 3

CHARACTERISTICS OF THE DRUG-INDUCED CONVULSIONS IN EXPERIMENT 2 (MEANS ± S.E.M.)

| Group | N | Convulsion 1 | 2 | 3 |
|---|---|---|---|---|
| Dose Administered (mg/kg) | | | | |
| Cocaine | 9 | 8.3 ± 0.6 | 7.7 ± 0.4 | 8.7 ± 0.9 |
| PTZ | 10 | 17.8 ± 1.7 | 18.4 ± 1.1 | 22.5 ± 2.6 |
| Clonus Duration (sec) | | | | |
| Cocaine | 9 | 13.9 ± 2.8 | 19.2 ± 6.4 | 37.4 ± 9.1*† |
| PTZ | 10 | 26.8 ± 3.9 | 17.1 ± 4.2 | 24.9 ± 5.2 |
| Clonus Intensity (rating) | | | | |
| Cocaine | 9 | 1.9 ± 0.1 | 1.9 ± 0.1 | 2.8 ± 0.2*† |
| PTZ | 10 | 2.9 ± 0.2 | 2.6 ± 0.2 | 3.1 ± 0.2 |

Specific comparisons using Tukey's (a) test: *significantly different from convulsion 1 at 0.05 level; †significantly different from convulsion 2 at 0.05 level.

TABLE 4

EFFECT OF DRUG TREATMENT ON KINDLING IN EXPERIMENT 2 (MEANS ± S.E.M.)

| Group | N | AD Threshold ($\mu$A) | AD's to Criterion Stage 2 | Stages 3–4 |
|---|---|---|---|---|
| Saline | 8 | 450 ± 52 | 9.6 ± 1.6 | 10.8 ± 1.7 |
| Cocaine | 9 | 339 ± 38 | 4.2 ± 0.4*† | 6.8 ± 1.7 |
| PTZ | 10 | 405 ± 29 | 8.4 ± 1.0 | 9.5 ± 1.2 |

Specific comparisons using Tukey's (a) test: *significantly different from saline group at 0.05 level; †significantly different from PTZ group at 0.05 level.

## RESULTS

Information concerning the three drug-induced convulsions is presented in Table 3. The dose administered was significantly higher for PTZ than for cocaine, $F(1,17)=53.15$, $p<0.001$, but there was no significant change in dose across the three convulsions, $F(2,34)=2.84$, and no significant interaction, $F(2,34)=1.65$. The cocaine and PTZ groups did not differ significantly in the total duration of the three convulsions (70.6±16.0 sec and 68.8±7.4 sec, respectively), $F(1,17)=0.01$. There was, however, a significant change in duration across the three convulsions, $F(2,34)=4.43$, $p<0.05$, and a significant interaction, $F(2,34)=3.73$, $p<0.05$. Specific comparisons indicated that animals in the cocaine group exhibited a significant increase in duration from the first to the third convulsion, while animals in the PTZ group did not. The rated intensity of the clonus was significantly higher for PTZ than cocaine, $F(1,17)=16.32$, $p<0.01$. There was also a significant change in intensity across the three convulsions, $F(2,34)=8.07$, $p<0.01$, with no significant interaction, $F(2,34)=1.80$. Specific comparisons indicated that cocaine animals exhibited a significant increase in intensity from the first to the third convulsion, while the smaller increase exhibited by the PTZ animals did not reach significance. The groups differed significantly in weight gained from the first convulsion to the first day of kindling, $F(2,24)=5.54$, $p<0.05$, with the cocaine group gaining significantly less weight (16±3 g) than the saline (29±2 g) or PTZ (26±3 g) groups. However, none of the animals lost weight, and all appeared healthy at the beginning of kindling.

The performance of the groups during kindling is presented in Table 4. There was no significant difference among the groups in AD threshold on the first day of kindling, $F(2,24)=1.94$. However, there was a highly significant difference among the groups in the number of AD's required to produce two consecutive stage 2 responses (forelimb clonus), $F(2,24)=6.80$, $p<0.01$, with animals in the cocaine group reaching this criterion significantly faster than either saline or PTZ animals. When measured to a stricter criterion of two consecutive stage 3 or 4 responses (rearing or falling), there was no longer a significant effect, $F(2,24)=1.69$.

A comparison of the animal's performance on the last day of kindling and at retest 21 days later is shown in Table 5. There was a highly significant difference among the groups in AD duration, $F(2,23)=9.82$, $p<0.01$, with cocaine animals having a significantly longer duration than saline animals. There was no significant change in AD duration from criterion day to retest day, $F(1,23)=0.06$, and no significant interaction, $F(2,23)=0.90$. The behavioral response to stimulation exhibited a significant difference among the groups, $F(2,23)=5.18$, $p<0.05$, no significant change across days, $F(1,23)=4.21$, and a significant interaction, $F(2,23)=7.68$, $p<0.01$. As Table 5 indicates, the behavioral response was

TABLE 5

COMPARISON OF THE RESPONSE TO STIMULATION AT CRITERION (LAST DAY OF KINDLING) AND AT RETEST IN EXPERIMENT 2 (MEANS ± S.E.M.)

| Group | N | AD Duration (sec) Criterion | Retest | Behavioral Rating Criterion | Retest |
|---|---|---|---|---|---|
| Saline | 7§ | 65.0 ± 7.8 | 54.4 ± 3.1 | 3.3 ± 0.3 | 3.6 ± 0.2 |
| Cocaine | 9 | 100.4 ± 9.0* | 102.4 ± 9.2* | 3.3 ± 0.2 | 2.2 ± 0.2*†‡ |
| PTZ | 10 | 77.6 ± 6.0 | 82.4 ± 8.4 | 3.6 ± 0.2 | 3.5 ± 0.2 |

Specific comparisons using Tukey's (a) test: *significantly different from saline group at 0.05 level; †significantly different from PTZ group at 0.05 level; ‡significantly different from criterion at 0.05 level.

§The data for one animal in the saline group were lost due to experimenter error.

similar for the three groups on the last day of kindling, but the cocaine group exhibited a significant decline at retest which was not seen in the other groups. The majority of cocaine animals exhibited only forelimb clonus at retest without rearing fully (stage 2); none of the animals in this group exhibited rearing and falling (stage 4).

## GENERAL DISCUSSION

The results of the present experiments confirm a previous finding [16] that one to three cocaine-induced convulsions facilitate subsequent kindling. This effect is not confined to a single anatomical site, since it works both for kindling of the amygdala [16] and of the OB (present experiments). Furthermore, it does not appear to be a transitory effect of the drug-induced convulsion, since a powerful effect is present when an 8-day waiting period is imposed between the last convulsion and the first stimulation of kindling. The strength of the effect is substantial. The earliest that a saline animal exhibited clonus in either of the present experiments was on the fourth day of kindling. In contrast, two of the nine animals which experienced three cocaine convulsions exhibited clonus the first time an AD was produced during kindling. This is the only instance in over 300 animals kindled in our laboratory in which the first AD of kindling has elicited clonus, and it suggests that the cocaine convulsions produced an effect similar to kindling so that the kindling process was already substantially completed when electrical stimulation began.

Facilitation of kindling was also produced by a lidocaine convulsion but not by PTZ convulsions, even if three convulsions were induced. This lack of an effect by PTZ cannot be attributed to differences in the duration or intensity of the convulsions induced by the drugs, since the PTZ convulsions equalled or exceeded the duration and intensity of cocaine convulsions. Consequently, it would appear that local-anesthetic-induced convulsions produce enduring functional changes in neuronal circuitry involved in kindling within the olfactory forebrain, while PTZ-induced convulsions do not. It is of course possible that a greater number of PTZ convulsions would have facilitated kindling, but it seems clear from the present results that at a minimum the two local anesthetics used are much more potent than PTZ in this regard. There is in fact considerable evidence of pro-convulsant effects of local anesthetics within the olfactory forebrain [3, 17, 18, 29, 34, 37], with some indication of preferential action within this area [8, 13, 15, 31]. In contrast, there is no evidence linking PTZ's convulsant action to this area of the brain. This raises the question of whether there might be other sites in the brain which would be affected strongly enough by three PTZ convulsions to facilitate subsequent kindling at that site. As previously stated, there are numerous reports of sensitization to the convulsant effect of PTZ with repeated administration, even when subconvulsant doses are used [2, 14, 19, 23, 24]. Furthermore, there is evidence of cross-sensitization between PTZ and other convulsant agents [1, 20, 25]. In addition, Cain [4] demonstrated that kindling at a variety of brain sites produced sensitization to the convulsant effects of PTZ. Thus PTZ participates in a number of different forms of convulsant sensitization, and has been shown to interact with kindling. Consequently, it seems plausible that its failure to facilitate kindling here is related at least in part to the locus of kindling used rather than to a qualitative difference in the sensitizing power of local anesthetic vs PTZ convulsions.

The characteristics of the drug-induced convulsions in Experiment 2 provide evidence of the differential effects of convulsions induced by cocaine and PTZ. Both the duration and rated intensity of the cocaine convulsions increased significantly from the first to third convulsion, while those characteristics of PTZ convulsions did not. The increased duration of the cocaine convulsions may be related to the increased AD duration seen at the end of kindling in the cocaine group in Experiment 2, an effect which was not evident for the PTZ group.

Some comment should be made concerning the failure of the lidocaine group in Experiment 1 and the cocaine group in Experiment 2 to exhibit significant facilitation of kindling to the "stricter" criterion of two consecutive stage 3 or 4 responses (rearing or falling). Occasionally animals kindled in the OB develop strong hind-limb clonus which precludes rearing and thereby prevents the animal from reaching this kindling criterion. This occurred in one animal in each of these groups. Thus although these animals rapidly reached the criterion for clonus (stage 2), the atypical form of their seizures caused them to receive the maximum or near-maximum score for AD's to the criterion for rearing or falling, greatly inflating their group means. If these animals are eliminated from consideration by dropping the highest scoring animal from every group, the two groups in question exhibit significant facilitation of kindling to the "stricter" criterion (Experiment 1: $F(3,23)=9.46, p<0.001$; Experiment 2: $F(2,21)=5.74, p<0.05$ with the group in question kindling significantly more rapidly than the saline group in each case). Thus we do not feel that the facilitation faded during the course of kindling. Rather it may be that the criterion of rearing or falling does not encompass all forms of fully kindled seizures that are seen with stimulation of the OB.

The data on the persistence of kindling in Experiment 2 also merit comment. While the AD duration of the cocaine group remained unchanged at retest, the rated behavioral response to stimulation declined significantly from criterion to retest in this group, reflecting a decrease in rearing. The other groups showed no such decline, suggesting that kindling was not as permanent in the cocaine group. This issue is difficult to assess, since animals in the cocaine group on the average experienced fewer AD's during kindling than animals in the other groups, and the role of this variable in the persistence of kindling has not been clearly established. It may also be that animals in the cocaine group were in effect being tested at a longer retest interval than the other groups, since in this group a major portion of the kindling effect was produced by cocaine-induced convulsions which occurred 8, 11 and 14 days prior to the first day of kindling. If in fact the kindling in the cocaine group is less permanent, its decline over time is very gradual. While the amount of rearing declined over a 21 day period without stimulation, there was no decline in AD duration or the presence of clonus. Thus the effect is on the whole quite persistent, although possibly not as persistent as kindling produced solely by electrical stimulation.

In summary, the present experiments demonstrate that convulsions induced by local anesthetics facilitate kindling of an olfactory forebrain site. The facilitation is robust and can be obtained for at least eight days after the last drug-induced convulsion. The same number of PTZ convulsions does not result in facilitation, suggesting that local-anesthetic-induced convulsions generate specific long-lasting functional changes within the olfactory forebrain which are not produced by all convulsants.

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