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Effect of Cocaine and Pentylenetetrazol on Cortical Kindling[1]

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STRIPLING, J. S. AND R. D. RUSSELL. *Effect of cocaine and pentylenetetrazol on cortical kindling*. PHARMACOL BIOCHEM BEHAV **23**(4) 573–581, 1985.—The effect of drug-induced convulsions on subsequent cortical kindling was studied in male Long-Evans rats. Animals experienced three intravenous infusions of physiological saline at 3 day intervals, or three convulsions induced by the infusion of cocaine or pentylenetetrazol (PTZ). Beginning eight days after the last infusion, all animals were kindled by stimulation of the anterior neocortex (area 6). PTZ-induced convulsions facilitated the development of both the behavioral convulsion and the electrographic seizure during cortical kindling, while cocaine-induced convulsions facilitated only the development of the electrographic seizure. Comparison of these results with previous research indicates that convulsions induced by these two drugs have long-lasting effects on brain function which differ both in their anatomical distribution and in the nature of the effects produced. These drugs also differed in their acute effects at subconvulsant doses on the expression of cortically kindled seizures. Cocaine (and lidocaine, another local anesthetic) substantially elevated afterdischarge (AD) threshold and inhibited the focal component of the cortically kindled seizure. PTZ had no significant effect on either of these variables but significantly increased AD duration. In addition to these drug effects, a substantial inhibitory effect on seizure expression was observed, both during kindling and afterwards, when ADs were elicited daily but not when they were separated by 3 days or more. This finding suggests that the large number of ADs typically required for cortical kindling may be due in part to daily stimulation.

Kindling Cortex Convulsion Cocaine Pentylenetetrazol Lidocaine Sensitization Rat

KINDLING is a form of sensitization to electrical stimulation of certain brain sites. With repetition, the effects of the stimulation gradually develop from a focal afterdischarge (AD) to a generalized electrographic seizure accompanied by a behavioral convulsion [14,29]. A similar form of sensitization, sometimes referred to as pharmacological or chemical kindling, can be seen as an enhanced convulsant response following the repeated administration of certain convulsant drugs [20, 24, 27, 35, 40]. Several studies have reported evidence of cross-sensitization between kindling and convulsant drugs, which can be manifested either as facilitation of kindling by previous exposure to convulsant drugs [8, 9, 10, 18, 37, 39], or as an enhanced convulsant response to a drug due to prior kindling [7, 9, 10, 17, 28]. The existence of cross-sensitization suggests that these two forms of sensitization are achieved in part via the same underlying mechanisms.

Pentylenetetrazol (PTZ) and local anesthetics such as cocaine and lidocaine are examples of convulsant drugs which have been found to exhibit cross-sensitization with kindling [7, 8, 9, 18, 37]. However, the manner in which these drugs produce cross-sensitization may differ. PTZ produces a continuum of convulsive behaviors ranging from facial twitches to myoclonic jerks to generalized convulsions. Cain [8] found that the repeated intraperitoneal administration of PTZ could facilitate subsequent kindling of the amygdala. Equivalent amounts of facilitation were produced by treatments which caused either several generalized convulsions or only facial twitches and myoclonic jerks. Thus generalized convulsions are not required for PTZ to produce effects which influence subsequent kindling. It has not yet been determined if the production of facial twitches and myoclonic jerks (and the electrographic spikes which accompany them) is required. In contrast to PTZ, cocaine and lidocaine typically produce a much sharper transition from non-convulsive behavior to generalized convulsions with little indication of intermediate forms such as myoclonic jerks. Available evidence indicates that, although repetition of a subconvulsive dose of cocaine can potentiate its behavioral stimulant effect [35], these drugs must produce generalized convulsions in order to facilitate subsequent kindling [18, 34, 37].

The preceding evidence suggests that both subconvulsive drug effects and drug-induced convulsions can play a role in cross-sensitization with kindling, and that their relative importance may depend upon the specific drug under investigation. Our laboratory has undertaken several studies to examine the effects of one of these factors, drug-induced convulsions, on subsequent kindling. Recently we reported that convulsions induced by intravenous infusions of cocaine or lidocaine, but not PTZ, facilitated subsequent kindling of the olfactory bulb [37]. This finding suggests that convulsions induced by local anesthetics have lasting effects on the olfactory forebrain not shared by convulsions induced by PTZ. It does not, however, permit the conclusion that local-anesthetic-induced convulsions facilitate subsequent

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TABLE 1
CHARACTERISTICS OF THE THREE DRUG-INDUCED CONVULSIONS
(MEANS ± S.E.M.)

	Group	
	Cocaine (N = 11)	PTZ (N = 13)
Convulsive Threshold (mg/kg)		
Convulsion 1	8.5 ± 0.4	19.3 ± 0.9
Convulsion 2	8.7 ± 0.4	19.4 ± 1.3
Convulsion 3	9.3 ± 0.5	23.0 ± 0.9*†
Convulsion duration (sec)		
Convulsion 1	18.5 ± 4.6	27.8 ± 2.3
Convulsion 2	27.0 ± 6.9	26.0 ± 2.7
Convulsion 3	43.5 ± 8.2*†	23.9 ± 3.3*
Total duration	89.0 ± 17.6	77.7 ± 7.7

Specific comparisons using the Newman-Keuls Test: * significantly different from Convulsion 1; † significantly different from Convulsion 2.

kindling while PTZ-induced convulsions do not. To assess this possibility one must first determine (1) whether convulsions induced by local anesthetics can facilitate kindling over a widespread area of the brain or only within the olfactory forebrain, and (2) whether PTZ-induced convulsions are capable of facilitating kindling if a different brain site is used. The present experiment was designed to address these issues by examining the effects of convulsions induced by intravenous infusions of cocaine or PTZ on subsequent kindling of the neocortex, which differs from kindling of the olfactory bulb and other limbic sites in both the rate of development and the form of the behavioral convulsions produced [5]. In addition, the effects of subconvulsive doses of these drugs on the expression of kindled cortical seizures was examined.

METHOD

Subjects

The subjects were male Long-Evans rats (Blue Spruce Farms) which weighed 345–440 g at 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.

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 200-μm-diameter monopolar stainless-steel electrodes were implanted bilaterally in the anterior neocortex (area 6) using the following coordinates: 2.5 mm anterior to bregma, 2.0 mm lateral of the midline, and 1.3 mm below the dura. In addition, stainless-steel screws were placed over the right anterior cortex (5.0 mm anterior to bregma and 1.7 mm lateral) and the left posterior cortex (3.0 mm posterior to bregma and 2.0 mm lateral) and a Silastic catheter [33] was implanted 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 an animal's home cage was placed in a clear acrylic recording chamber enclosed within a larger chamber for visual and acoustic isolation. The cables used for recording and stimulation were attached to a BRS/LVE slip-ring commutator mounted on a counterbalanced arm, allowing the animal full freedom of movement. Drug-induced electrographic seizures were recorded using a cable containing a field-effect transistor circuit to minimize movement artifacts [32]. The animal's behavior was monitored via closed-circuit TV and recorded on video tape for subsequent analysis. A Grass S48 stimulator and PSIU6 stimulus isolation unit were used for stimulation and a Beckman R611 polygraph for recording. Intravenous infusions were made using a Harvard 975 infusion pump.

Procedure

The basic design of the experiment was as follows. After recovery from surgery the animals were randomly divided into three groups. Animals in the cocaine and PTZ groups experienced three convulsions produced by cocaine or PTZ at 3-day intervals, while animals in the saline group received physiological saline. Beginning on the eighth day after the last drug treatment, all animals were kindled to criterion by electrical stimulation of the neocortex. Animals were then tested for the effects of subconvulsive doses of cocaine, lidocaine, and PTZ on the expression of fully kindled seizures.

The drug-induced convulsions were produced by intravenous infusion of 20 mg/ml cocaine hydrochloride or 40 mg/ml PTZ at a rate of 0.25 ml/min. Each infusion was continued until the onset of an electrographic seizure and behavioral convulsion. Saline animals received infusions of physiological saline of comparable duration.

Kindling was produced by stimulation of the left cortex

via the depth electrode using a 2-sec train of monopolar negative square-wave pulses of 0.2 msec duration at a frequency of 50 pulses/sec. The cortical screws over the left posterior cortex and right anterior cortex were used as references for stimulation and recording, respectively. On the first day of kindling the afterdischarge (AD) threshold of the stimulation site was determined by a stairstep procedure. Each animal was initially stimulated at a current intensity of 50 μA. Every 60 sec the current intensity was increased 50 μA and the stimulation repeated until an AD was produced. Animals not exhibiting an AD by 800 μA were eliminated from the experiment. Beginning on the second day of kindling each animal was stimulated once daily at its AD threshold as determined on Day 1. If this stimulation did not elicit an AD, the current intensity was increased by 50 μA and the stimulation repeated until an AD was elicited. After the 22nd day of kindling the interval between stimulations was increased to 72 hr to dissipate inhibitory effects which had become apparent at the 24-hr stimulation interval. Animals were kindled to a criterion of two consecutive ADs $\geq$30 sec accompanied by clonus. Animals reaching criterion before the 26th AD continued to receive stimulation to that point to permit an evaluation in all animals of any effects on performance caused by the change in stimulation interval. Stimulation was terminated after the 50th AD for animals which had not yet reached criterion. Animals which had not shown any sign of a kindling effect by this point (i.e., all ADs $\leq$15 sec) were eliminated from the experiment. The kindling phase of the experiment was carried out by an experimenter who was unaware of the drug treatment each animal had received.

Following kindling, animals which had reached criterion were used to examine the expression of previously kindled seizures following the intraperitoneal injection of saline, 20 mg/kg cocaine hydrochloride, 20 mg/kg lidocaine hydrochloride, and 12 mg/kg PTZ. These doses were approximately the highest which could be administered without risk of a drug-induced convulsion in kindled animals. Each animal received each drug once, with a 4-day interval separating successive drug tests. The order of drug administration was counterbalanced across animals. Beginning 8 min after injection on each test day the AD threshold was determined by the same procedure used at the beginning of kindling, with an upper limit of 1200 μA.

Of 41 animals which began the experiment, one PTZ and two cocaine animals died during the drug-induced convulsions, one saline animal died during kindling, and another saline animal was eliminated after failing to exhibit an AD on the first day of kindling. In addition, one saline and one cocaine animal were eliminated for failure to exhibit an AD of 15 sec or more during 50 days of kindling. This left 34 animals in the study. At the end of the study all electrode placements were verified histologically using the Prussian blue method [36].

Drug effects were assessed by analysis of variance followed by specific comparisons using the Newman-Keuls test [41]. Variables exhibiting pronounced non-homogeneity of variance across conditions were subjected to logarithmic transformation prior to analysis.

RESULTS

Information concerning the three drug-induced convulsions is presented in Table 1. PTZ had a significantly higher convulsive threshold than cocaine, $F(1,22) = 247.40$, $p<0.001$, and there was a significant change in threshold across convulsions, $F(2,44) = 8.32$, $p<0.01$. Although both groups exhibited an increase in threshold from the first convulsion to the third, with no significant interaction, $F(2,44) = 1.56$, specific comparisons indicated that the increase reached significance only in the PTZ group. The two groups did not differ significantly in the total duration of the three convulsions, $F(1,22) = 0.38$, but there was a significant change in duration across convulsions, $F(2,44) = 5.83$, $p<0.01$, and a significant interaction, $F(2,44) = 14.11$, $p<0.001$. Specific comparisons indicated that the cocaine-induced convulsions increased significantly in duration from the first to third convulsion, while there was a small but significant decrease in the PTZ group.

The kindling produced by electrical stimulation of the cortex followed the basic pattern which has been described by others [5,30]. From the outset animals exhibited a brief focal seizure characterized by clonus and loss of righting. Some (but not all) animals exhibited tonus during the loss of righting. As kindling progressed, there was a gradual increase in the duration of the AD and clonus, while the loss of righting remained restricted to the early portion of the seizure. Rearing and falling appeared during the latter part of clonus, although falling was not seen in all animals. By the 22nd day of kindling it was apparent that some animals which had received drug-induced convulsions were responding erratically to stimulation, exhibiting a long AD on one day followed by a short one on the next. In addition there was an elevation of AD threshold in many animals. These events appeared to represent a build-up of inhibitory effects produced by the daily stimulation, and consequently the interval between ADs was increased to 72 hr, which substantially improved performance (see Fig. 1).

The drug-induced convulsions had no significant effect on AD threshold at the beginning of kindling, $F(2,31) = 1.05$ (see Fig. 1B). Their effect on the progress of kindling is shown in Fig. 2. This effect was analyzed in several ways. The development of the behavioral response was assessed by examining kindling to a criterion of two consecutive ADs with clonus and rearing (falling was not examined because it was not present in all animals). There was a significant effect of the drug treatment, $F(2,31) = 5.07$, $p<0.05$, with the PTZ group kindling significantly faster than either the saline or cocaine groups (Fig. 2A). A different pattern was seen when AD development was examined, as measured by the rate of kindling to a criterion of two consecutive ADs $\geq$30 sec. Again there was a significant drug effect, $F(2,31) = 7.09$, $p<0.01$, but here both drug groups kindled significantly faster than the saline group, with no significant difference between themselves (Fig. 2B). A closer look was taken at the effect of the drug-induced convulsions on AD development by examining AD duration on the criterion day for the preceding analysis (animals which did not reach this criterion within the 50-AD limit were excluded from this analysis). A significant effect was again found, $F(2,25) = 9.74$, $p<0.001$, with cocaine animals having a significantly longer AD than either saline or PTZ animals, which did not differ significantly from each other (Fig. 2C). Thus while both drug groups reached the 30-sec AD criterion at about the same rate, the actual AD duration was substantially longer in the cocaine group at this point.

Following the completion of kindling, 24 animals which had reached criterion were used to examine the effect of subconvulsive doses of cocaine, lidocaine, and PTZ on the expression of cortically kindled seizures (see Fig. 3). There

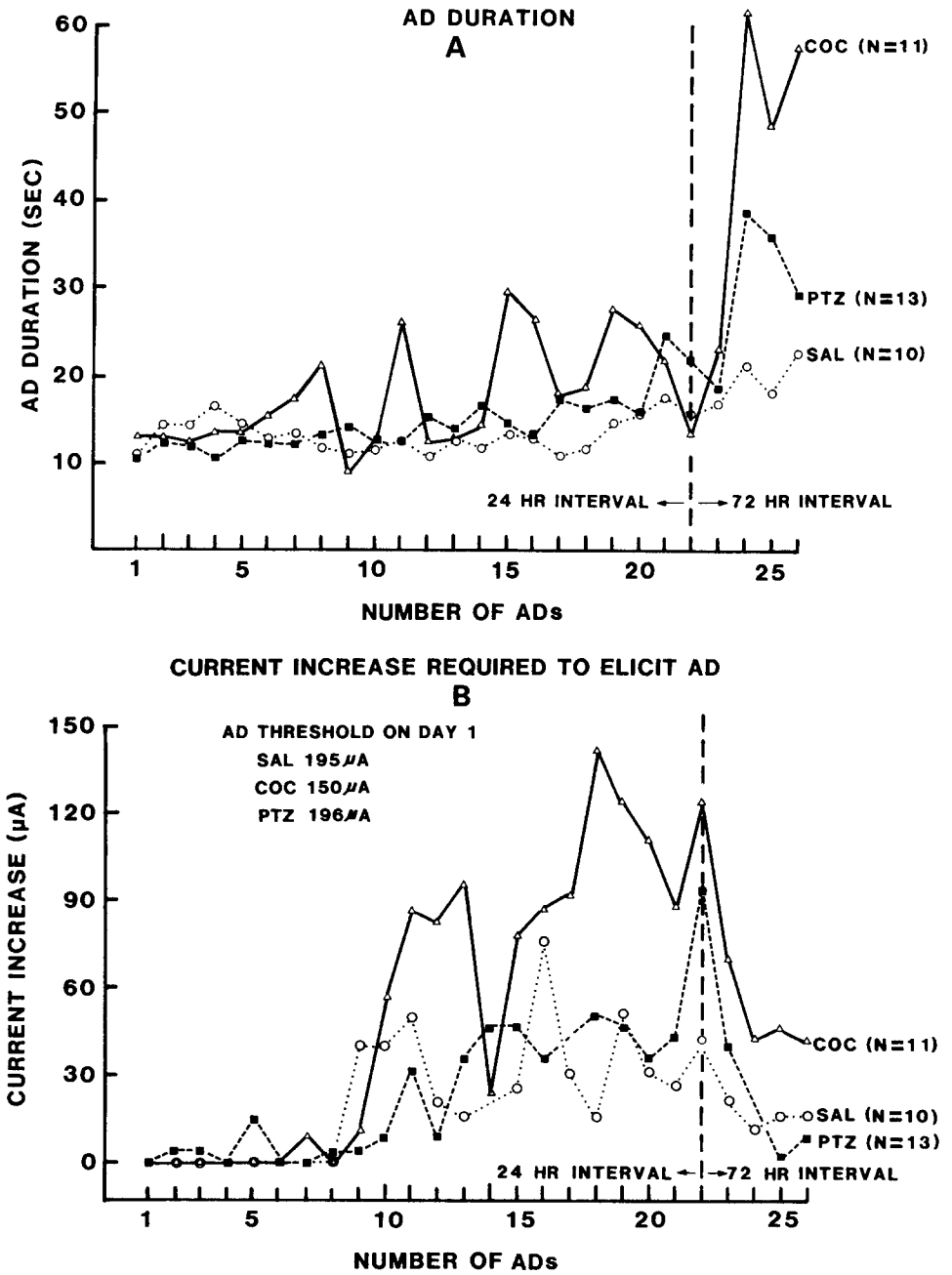

FIG. 1. A: Duration of the first 26 ADs elicited during kindling in the SAL (saline), COC (cocaine), and PTZ (pentylenetetrazol) groups. The instability in the curve for the cocaine group is due to extreme fluctuations in the scores of individual animals, with a long AD often followed the next day by an unusually short one. B: Change in AD threshold across the first 26 ADs as reflected by the current increase required to elicit an AD (stimulation began each day at the animal's original AD threshold). After the 22nd AD the interval between ADs was increased from 24 to 72 hr, greatly reducing the inhibitory effects seen prior to that point.

was a significant drug effect on AD threshold, $F(3,69) = 30.54, p<0.001$, with both cocaine and lidocaine producing a significantly higher AD threshold than saline. The small decrease in threshold seen following PTZ did not reach significance (Fig. 3A). Drug effects on seizure duration were analyzed using the 17 animals which had ADs > 10 sec in all four drug conditions (three animals did not have an AD in the cocaine or lidocaine conditions within the 1200 μA limit, and four others had an AD only a few seconds long). AD duration was significantly affected by the drug treatment, $F(3,48) = 7.42$, $p<0.001$, with PTZ significantly elevating AD duration above all other conditions. No other comparisons were significant (Fig. 3B). The focal component of cortically kindled seizures was assessed by the duration

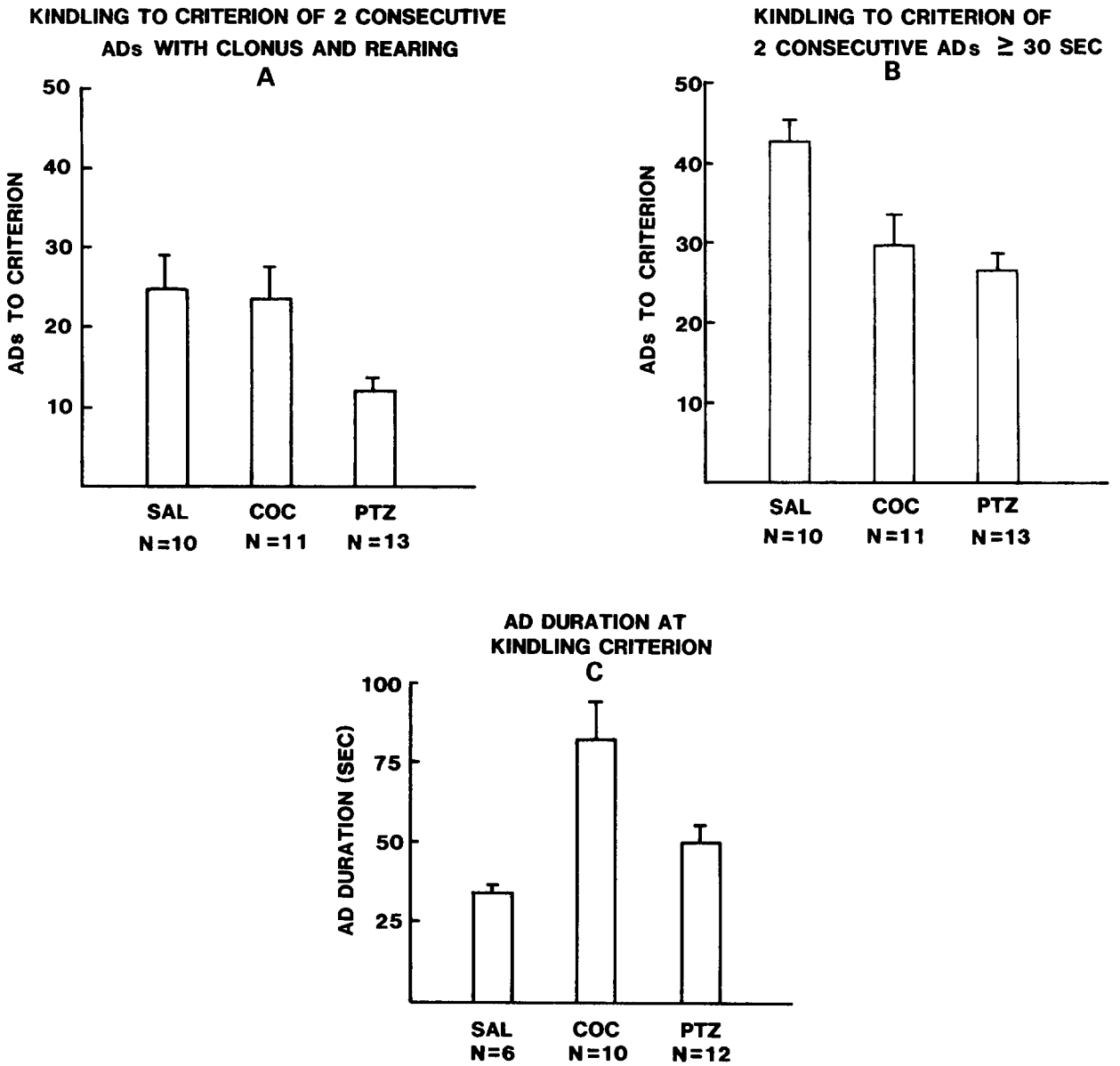

FIG. 2. The effect of the drug-induced convulsions on (A) the development of behavior during kindling, as measured by the appearance of rearing, (B) the development of the AD to a length of 30 sec or more, and (C) the actual length of the AD at the point at which it had grown to at least 30 sec in length (note that 1 cocaine, 1 PTZ, and 4 saline animals did not reach this criterion and were therefore excluded from this analysis). Data are means+S.E.M.

of the loss of righting which normally occurs within a few seconds of stimulation. There was a significant drug effect on this variable, $F(3,48) = 28.98$, $p<0.001$, with both cocaine and lidocaine significantly reducing (and in many cases eliminating) loss of righting (Fig. 3C).

The majority of the animals used in the post-kindling drug tests had experienced convulsions induced by cocaine or PTZ prior to kindling, which might have affected their response during the drug tests. Consequently the preceding analyses were repeated using only animals which had received saline prior to kindling (n = 6). In each case the drug effects exhibited the same pattern seen in the overall analysis. The effects reached statistical significance for AD threshold, $F(3,15) = 10.02$, $p<0.001$, and loss of righting,

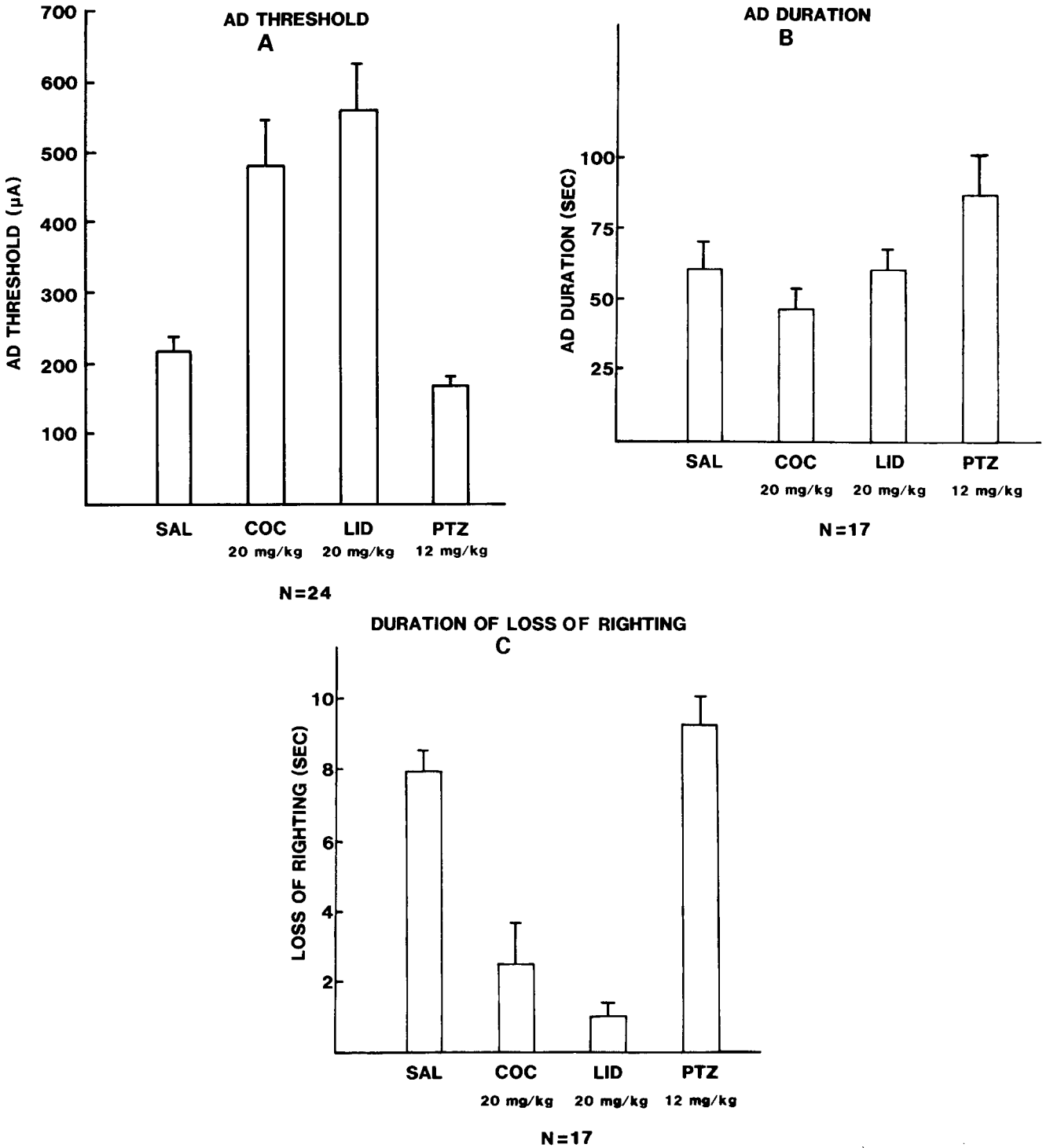

FIG. 3. The effect of intraperitoneal injections of saline (SAL), 20 mg/kg cocaine HCl (COC), 20 mg/kg lidocaine HCl (LID), and 12 mg/kg pentylenetetrazol (PTZ) on *A*) AD threshold, (B) AD duration, and (C) loss of righting in animals previously kindled by cortical stimulation. Data are means+S.E.M. The 24 animals used to assess AD threshold included 6 animals which had been in the saline condition during kindling, 8 which had experienced cocaine-induced convulsions, and 10 which had experienced PTZ-induced convulsions. The analysis of AD duration and loss of righting used only the 17 animals which had AD durations >10 sec in all four drug conditions.

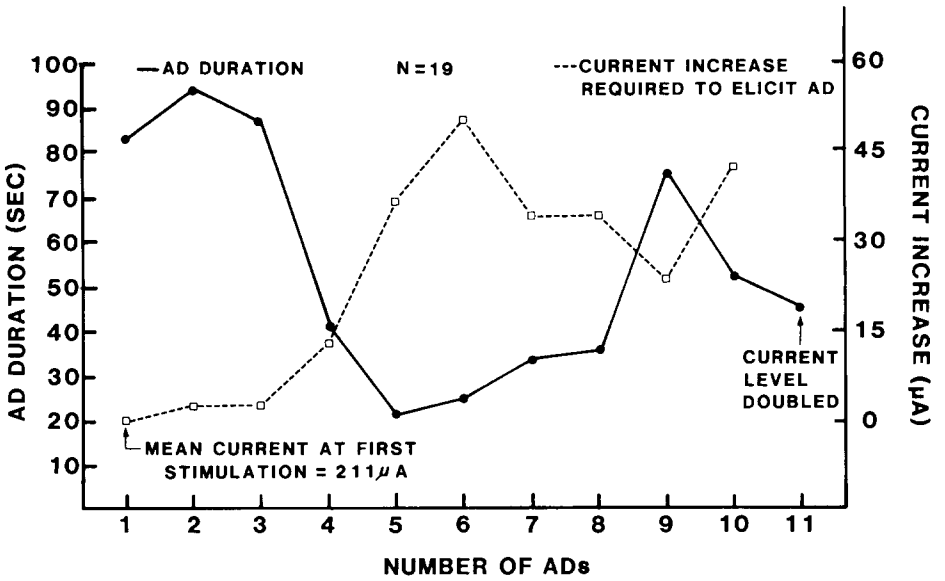

FIG. 4. The effect of daily stimulation of the cortex on AD duration and AD threshold (as reflected by the current increase required to elicit an AD) in previously kindled animals. The stimulation procedure for the first 10 days paralleled that used during kindling; on Day 11 the stimulation current was doubled for each animal.

$F(3,15) = 10.90$, $p<0.001$, and approached significance for AD duration, $F(3,15) = 3.08$, $p<0.07$. The size of each of these effects, as measured by eta-squared (which reflects the proportion of the total variance accounted for by the experimental treatment), was actually larger for the saline animals alone than for all animals combined. Thus the drug effects reported above do not appear to be an artifact of prior drug treatment.

Following completion of the planned experiments, two post-hoc experiments were run to clarify the interpretation of the results obtained. The first of these was designed to determine whether the substantial differences across drug conditions in the current intensity required to trigger a kindled seizure could have accounted for the drug effects shown in Fig. 3. The AD threshold was first determined in 22 animals by the procedure used previously. Each animal was then tested three times at 4-day intervals for the expression of kindled seizures following stimulation at 100%, 150%, and 200% of its AD threshold. This manipulation had no significant effect on either AD duration or loss of righting.

The second post-hoc experiment was conducted to investigate further the inhibitory effects seen during kindling at a 24-hr stimulation interval. Nineteen animals which had received stimulation at 4-day intervals in the previous two experiments were returned to the conditions used during the first 22 days of kindling: daily stimulation at their original AD thresholds as determined on the first day of kindling. As in the original kindling, animals not exhibiting an AD were stimulated repeatedly at increasing current intensities until an AD occurred. This procedure was continued for 10 days. On the eleventh day each animal was stimulated at twice its original AD threshold. The results are shown in Fig. 4. There was a significant change in AD duration across the 11 days of stimulation, $F(10,180) = 5.89$, $p<0.001$, and a significant change in the amount of current required to elicit an AD during the first 10 days, $F(9,162) = 4.88$, $p<0.001$. Inspection of Fig. 4 reveals that AD duration declined dramatically during the first 5 days, indicating that ADs elicited at 24-hr intervals result in a cumulative inhibitory process which greatly hinders the expression of kindled seizures. AD duration then partially recovered its original length over the next 4 days. This suggests that the strength of the inhibitory effect produced by an AD is related to its duration, so that there is some recovery of the seizure after it has been reduced to a short AD for several days. All animals exhibited an AD at their original AD threshold on the first day, but over the next 5 days the current required to elicit an AD increased substantially. The decrease in AD duration was not dependent upon the changes in current intensity, because a significant decline was present in 7 animals which did not require a current increase during the 11 days of stimulation, $F(10,60) = 3.48$, $p<0.01$. The doubling of current intensity on the eleventh day was unable to increase AD duration.

DISCUSSION

Convulsions induced by either cocaine or PTZ facilitated the development of cortical kindling in this experiment, but the pattern of facilitation differed for the two drugs. PTZ-induced convulsions facilitated the development of both the behavioral convulsion and the electrographic seizure (Fig. 2A and 2B), while cocaine-induced convulsions facilitated only the development of the electrographic seizure, but did so more effectively than PTZ-induced convulsions (Fig. 2B and 2C). In a previous experiment which utilized drug treatments identical to those used in the present experiment, Stripling and Hendricks [37] found that kindling of the olfactory bulb was facilitated by convulsions induced by cocaine but not by PTZ. A comparison of the results of these two experiments indicates that the effects of convulsions induced by the two drugs are clearly different. Cocaine-induced convulsions facilitate the development of both the behavioral convulsion and electrographic seizure produced

by kindling of the olfactory bulb, but facilitate only the development of the electrographic seizure in cortical kindling. In contrast, PTZ-induced convulsions have no effect on olfactory bulb kindling but facilitate the development of both the behavioral and electrographic components of cortical kindling. This comparison demonstrates that convulsions induced by cocaine and PTZ differ both in the anatomical distribution of their effects and in the types of functional changes they produce.

In general, the results of these experiments indicate that convulsions produced by different drugs can have different long-term effects on brain function, and that these effects can have different anatomical profiles. These results also emphasize the usefulness of kindling as a probe for determining the anatomical distribution of cross-sensitization produced by drugs or other agents.

Because these two experiments provided evidence of cross-sensitization between kindling and both cocaine-induced and PTZ-induced convulsions in at least one of the sites tested, one might expect that some sign of sensitization to the drugs themselves would be seen during the three drug-induced convulsions. Yet no sign of sensitization to PTZ was evident in either experiment as measured by convulsive threshold or convulsion duration. In both experiments there was limited evidence of sensitization during cocaine-induced convulsions, which exhibited an increase in duration but no drop in convulsive threshold. These findings are puzzling, because other experiments which have demonstrated cross-sensitization between drug-induced convulsions and kindling have also found evidence of drug sensitization [8, 9, 10, 18, 39]. Sensitization to the convulsant effects of cocaine [26,35] and PTZ [1, 16, 20, 24] has been repeatedly demonstrated following intraperitoneal administration, and consequently the lack of sensitization found in the present experiment and elsewhere [11, 21, 22, 37] following intravenous administration may indicate that sensitization is difficult to produce or measure using this route of administration. This possibility is supported by Nutt *et al.* [23], who found that sensitization produced by repeated intraperitoneal administration of picrotoxin or PTZ had no detectable effect on the convulsive threshold to an intravenous infusion of these drugs. Another possible explanation is that sensitization was present but not easily detected in the present experiment due to transitory inhibitory effects of the convulsions which did not dissipate within the 3-day interval between convulsions but were absent at the start of kindling 8 days later. Finally, it may be that convulsive threshold is not altered by the drug-induced changes which facilitate kindling. In this regard it is worth noting that the AD threshold at the start of kindling was not affected by the drug-induced convulsions. Regardless of the reason, it is evident from the performance of the PTZ group in the present experiment that repeated drug-induced convulsions can cause long-term changes in brain function without comparable changes in the expression of the drug-induced convulsions themselves.

The post-kindling drug tests revealed that cocaine and PTZ differ not only in the long-term effects of the convulsions they produce, but also in their acute effects on the expression of kindled cortical seizures. Cocaine's effects paralleled those of lidocaine, another local anesthetic, while PTZ's effects followed an entirely different pattern. Indeed, none of the three dependent variables analyzed were affected in the same way by both PTZ and the two local anesthetics.

The local anesthetics had a larger effect on the AD threshold of cortically kindled seizures than has been previously found for ADs triggered from a limbic site [38]. In the present experiment AD threshold was elevated 120% by cocaine. A previous experiment using the same stimulation procedure found that the same dose of cocaine increased AD threshold in the olfactory bulb by only 19% [38]. Similarly, Burnham *et al.* [6] found that procaine, another local anesthetic, was significantly more effective in suppressing ADs triggered from the cortex than those triggered from the amygdala.

Bowyer *et al.* [3], using a single suprathreshold stimulation to trigger an AD, reported that lidocaine decreased AD duration in cortically kindled seizures. In the present experiment neither lidocaine nor cocaine significantly affected AD duration, but both drugs powerfully elevated AD threshold. This suggests that the effect reported by Bowyer *et al.* [3] represents an elevation of AD threshold rather than a reduction of the duration of ADs once they have been successfully triggered.

The focal component of the cortically kindled seizure (as measured by the loss of righting) was powerfully and selectively inhibited by the local anesthetics in the present experiment. A similar effect has been reported for procaine [30,31], suggesting that this is an effect common to all local anesthetic drugs. This effect might be accomplished either by suppressing the focal seizure (or its influence over the body musculature), or by facilitating the spread of seizure activity to brain sites which participate in the expression of the clonic cortico-generalized seizure, causing it to supersede the focal seizure. The latter possiblity is supported by the reduction in clonus latency produced by cocaine and lidocaine in limbic kindling [36], which appears to reflect a facilitation of the propagation of seizure activity [19] from the site of stimulation to areas responsible for the motor seizure.

In the present experiment PTZ significantly increased the AD duration of cortically kindled seizures. Similar findings have been reported for amygdaloid kindled seizures [2,4]. Bowyer *et al.* [3], using a smaller number of animals than the present experiment, found only a small and nonsignificant increase in the AD duration of cortically kindled seizures following the administration of PTZ.

One of the most striking differences between limbic and cortical kindling is the rate at which they occur. In the present experiment the expression of cortical kindling was greatly impeded by daily stimulation and was clearly visible only when a 3-day interval between stimulations was used. This finding and the data represented in Fig. 4 indicate that substantial inhibitory effects follow each seizure during cortical kindling which require more than 24 hr to dissipate. It should be emphasized that the present experiment used stimulation at the original AD threshold, and that other experiments using higher current intensities might not show this effect as clearly. Although limbic kindling produces similar inhibitory effects which can also last 24 hr or longer ([12, 13, 15, 25], Russell and Stripling, manuscript in preparation), these effects are too weak to prevent the occurrence of rapid kindling with daily stimulation. Whether the inhibitory effects seen in cortical kindling impair the development of kindled seizures as well as their expression cannot be determined with certainty from the present experiment, but the possibility is certainly worth considering that the large number of ADs required for cortical kindling might be substantially reduced with a stimulation interval greater than 24 hr.

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