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Effect of Cocaine and Lidocaine on the Expression of Kindled Seizures in the Rat[1]

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STRIPLING, J. S. AND C. HENDRICKS. *Effect of cocaine and lidocaine on the expression of kindled seizures in the rat.* PHARMAC. BIOCHEM. BEHAV. **14**(3) 397–403, 1981.—The effect of cocaine and lidocaine on the expression of kindled seizures was studied in male Long-Evans rats. Animals were implanted with an electrode in either the olfactory bulb, prepyriform cortex, or basolateral amygdala and kindled by daily electrical stimulation. Each animal was then tested for the expression of kindled seizures following the intraperitoneal administration of saline, 20 mg/kg cocaine hydrochloride, or 20 mg/kg lidocaine hydrochloride. During testing the implantation site was stimulated every 60 sec at increasing current levels until an afterdischarge was elicited. Each animal was tested once under each drug at 96 hr intervals. The order of drug administration was counterbalanced across animals. Neither cocaine nor lidocaine had a significant effect on afterdischarge threshold. Both drugs significantly reduced the latency for clonus to occur following stimulation, a measure presumably related to the propagation of afterdischarges from the site of stimulation to other brain areas. In addition both cocaine and lidocaine significantly reduced the rated behavioral response to the stimulation due to a decrease in rearing and falling. Because they occurred with both cocaine and lidocaine, these effects appear to be of local anesthetic origin. In contrast, only cocaine significantly reduced afterdischarge duration, and only lidocaine significantly reduced clonus intensity. With the possible exception of clonus latency, these effects were present at all electrode sites studied. The results indicate that cocaine has pronounced effects on the expression of seizure activity in the olfactory forebrain, some of which are due to its local anesthetic action, and some not.

Cocaine Lidocaine Kindling Olfactory bulb Prepyriform cortex Amygdala Rat

IN addition to its well-known psychomotor stimulant action, cocaine has pronounced effects on seizure susceptibility. At high doses it produces a characteristic form of clonic convulsion [7,31]. In lower doses it has the opposite effect, inhibiting convulsions produced by a variety of convulsive agents such as pentylenetetrazol [34], electroconvulsive shock [33], audiogenic seizures [1], and hyperbaric oxygen [12].

The mechanism underlying these effects is not well understood. Cocaine has two major known pharmacological actions: it facilitates monoaminergic transmission by blocking the uptake of dopamine, norepinephrine, and serotonin into presynaptic terminals [24,25], and it acts as a local anesthetic [5]. The convulsant effect of cocaine would appear to be primarily a local anesthetic effect, since other local anesthetics produce highly similar convulsions [18, 35, 36]; however there may also be monoaminergic involvement, since reserpine has been reported to prevent cocaine convulsions [7,28]. Cocaine's anticonvulsant effect also may involve both of its pharmacological actions. Other local anesthetics are effective anticonvulsants [30], and there is considerable evidence for an inhibitory role of the monoamines, and particularly norepinephrine, in the occurrence of convulsions [9, 26, 37].

Cocaine has a pronounced electrophysiological effect within the olfactory forebrain which may provide a clue to the origin of its convulsant action: at doses approaching the convulsive threshold it produces bursts of high-amplitude sinusoidal potentials at a frequency of 20–50 Hz ("cocaine spindles") [7, 8, 32]. A similar effect is produced by other local anesthetics such as lidocaine [23, 35, 36]. Because this activity precedes the occurrence of convulsions and because its high amplitude presumably reflects synchronous activity in a large number of neurons, it has been suggested that the drug-induced spindle activity is a representation of neural events which may eventually culminate in a convulsion [9, 35, 36]. This line of evidence implies the involvement of the olfactory forebrain in cocaine's effect on seizure susceptibility.

Kindling is the gradual development of electrophysiological seizure activity and behavioral convulsions due to repeated electrical stimulation of the brain [10]. It is most readily produced in areas of the limbic system and involves both the lowering of the electrophysiological afterdischarge threshold at the site of stimulation and the enhanced propagation of this activity to other parts of the brain [19,20]. There is evidence that cocaine affects this phenomenon, but the nature of its effect is not yet clear. It has recently been

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reported by Lesse and his colleagues [13,14] that cocaine reduces the afterdischarge threshold at the site of stimulation and increases the speed of afterdischarge propagation from the site of stimulation to other brain sites during kindling of the amygdala or hippocampus in the cat. In contrast, Matsuzaki and Misra [15] have reported that cocaine produces an elevated threshold for afterdischarges elicited by stimulation of the amygdala or hippocampus in the cat.

There is also the question of whether any effect of cocaine on kindling should be attributed to its monoaminergic or local anesthetic action, since both local anesthetics and monoaminergic manipulations have been reported to affect kindling. Procaine facilitates kindling of the amygdala when administered prior to each electrical stimulation [22], and a number of studies indicate that the monoamines, and particularly norepinephrine, exert an inhibitory influence on the development of kindling [3, 4, 6, 16].

The present experiment was designed to explore the effect of cocaine on the expression of seizures previously kindled at various sites within the olfactory forebrain and to determine whether a similar effect could be produced by a local anesthetic without cocaine's monoaminergic action. Three stimulation sites were chosen for comparison: the olfactory bulb, prepyriform cortex, and amygdala. Lidocaine was chosen as a local anesthetic for comparison with cocaine, since lidocaine and cocaine are approximately equal in local anesthetic potency as measured by the production of spindles in the olfactory forebrain (Stripling, manuscript in preparation).

METHOD

Subjects

The subjects were 36 male Long-Evans rats (Blue Spruce Farms) which weighed 275–375 g at the time of surgery. They were housed individually in clear plastic cages (floor: 26.7 cm×48.3 cm; height: 20.3 cm), and were maintained on a 12 hr/12 hr light/dark cycle with food and water freely available throughout the experiment. The animals were gentled by daily handling before the experiment.

Procedure

Surgery was performed under sodium pentobarbital (42.5 mg/kg) and chloral hydrate (100 mg/kg) anesthesia. Each animal was implanted with a single monopolar electrode (200 μm diameter enamel-insulated stainless steel wire) in either the left olfactory bulb (OB), the left prepyriform cortex (PPC), or the left basolateral amygdala (AMYG). During stereotaxic surgery the tooth bar was 5 mm above the plane of the ear bars. The coordinates for the OB electrode were 9.1 mm anterior to bregma, 1.2 mm lateral, and 1.5 mm below the dura. To reach the remaining two sites, the electrode was angled laterally 14 degrees during implantation. For the PPC a hole was drilled in the skull 2.4 mm anterior to bregma and 2.8 mm lateral, and the electrode lowered 7.8 mm below the dura (final lateral coordinate=4.7 mm). For the AMYG a hole was drilled 0.8 mm posterior to bregma and 3.1 mm lateral, and the electrode lowered 8.0 mm below the dura (final lateral coordinate=5.0 mm). A single stainless steel screw placed over the right anterior cortex (2.5 mm anterior to bregma, 2.0 mm lateral) served as a reference for stimulation and recording. The animals were allowed a minimum of 14 days postoperative recovery before kindling began.

All data were collected between the fourth and eighth hours of the 12-hr light period. During data collection the animal remained within its home cage, which was inserted into a clear acrylic recording chamber enclosed within a Faraday cage and a larger plywood chamber for visual and acoustic isolation. A cable leading from the animal's head to a slip-ring commutator (BRS/LVE) mounted on a counterbalanced arm was used for stimulation and recording; this arrangement allowed the animal full freedom of movement within its cage. Behavior was monitored via closed circuit TV, and behavioral responses to stimulation were 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 was used to record afterdischarges following stimulation with filters set at 5–100 Hz. During stimulation a relay automatically disconnected the animal from the polygraph and connected it to the stimulator.

During all stages of the experiment stimulation consisted of 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 stimulation site was determined as follows. Each animal was initially stimulated at a current level of 100 μA. The current was increased 50 μA and the stimulation repeated every 60 sec until an AD was observed. On the following and all subsequent days of kindling each animal was stimulated once at 50 μA above its AD threshold as determined on the first day. The behavioral response to stimulation was measured on a 5-point rating scale: (1) rhythmic head nodding; (2) chewing movements; (3) forelimb clonus; (4) rearing; or (5) falling. When forelimb clonus occurred, its intensity was measured on a 4-point rating scale: (1) mild; (2) moderate; (3) vigorous; or (4) severe. Each animal was stimulated daily until a stage 4 or 5 response to stimulation occurred on 2 consecutive days. At that point the animal was considered to be kindled and the daily stimulation was terminated. Animals which did not kindle within 21 days of stimulation were discarded from the experiment.

Following kindling each animal was tested for the effect of physiological saline, 20 mg/kg cocaine hydrochloride, or 20 mg/kg lidocaine hydrochloride on the expression of the previously kindled seizures. The doses of cocaine and lidocaine were chosen to be well below the convulsive threshold, which falls in the range of 40–80 mg/kg for most animals. Testing began 96 hr after an animal reached the kindling criterion. Each animal was tested once under each drug at 96 hr intervals. The order of drug administration was counterbalanced across animals within each electrode group.

The test procedure was as follows. The animal was administered the drug via intraperitoneal injection and placed within the recording chamber. At 8 min post-injection the animal was stimulated at a current level of 50 μA. If an AD which persisted for a minimum of 2 sec following stimulation was evoked at the stimulation site, the animal's AD threshold was defined to be 50 μA. If no AD occurred, the animal was stimulated at 60 sec intervals at increasing current levels until such an AD did occur. On three occasions during the experiment, an AD was not accompanied by behavioral clonus. In these cases stimulation was continued at 60 sec intervals and increasing current levels until clonus occurred. In all cases, the AD threshold was defined as the lowest current level at which an AD of 2 sec duration or longer occurred, a procedure which should give an accurate estimate of AD threshold despite the fact that most animals received repeated sub-threshold stimulation [17].

TABLE 1

MEAN PERFORMANCE ± SEM OF THE OLFACTORY BULB (OB), PREPYRIFORM CORTEX (PPC), AND AMYGDALA (AMYG) GROUPS DURING KINDLING

	Electrode Site		
	OB (N=11)	PPC (N=10)	AMYG (N=8)
AD Threshold (μA) on the First Day of Kindling	345.5 ± 47.4	105.0 ± 5.0*	181.3 ± 21.0*†
Number of Days to Reach Kindling Criterion	10.7 ± 1.3	11.7 ± 1.2	10.4 ± 0.7

Specific comparisons using Ryan's procedure:
*Significantly different from OB at 0.05 level or beyond.
†Significantly different from PPC at 0.05 level or beyond.

In order to minimize any differences among the groups in the time following injection when AD's were triggered, different stimulation sequences were used for the three groups. Stimulation was increased by increments of 50 μA in the OB group, by 10 μA in the PPC group, and by 25 μA in the AMYG group. These sequences were based on the differences in AD threshold among the groups on the first day of kindling.

After an animal had been tested once under each drug, the animal's electrode position was determined using the Prussian Blue technique. The animal was deeply anesthetized with sodium pentobarbital and perfused through the heart with physiological saline followed by a solution of 10% Formalin, 1% glacial acetic acid, and 2% potassium ferrocyanide. An anodal current of 75 μA was then passed through the electrode for 5 sec. The brain was removed and placed in a solution of 10% Formalin and 30% sucrose for several days. The brain was then embedded in gelatin and returned to the solution for several more days. Frozen sections were cut at 50 μm and stained with cresyl violet for histological analysis.

The rate of kindling was analyzed by a 1-factor between-subjects analysis of variance [39]. Drug effects on the expression of kindled seizures were analyzed by 2-factor analyses of variance (electrode group×drug) with repeated measures on one factor [39]. Significant effects were followed by specific comparisons using the Tukey (a) procedure [39]. Due to pronounced non-homogeneity of variance across electrode groups, the data on current thresholds for AD's or behavior were analyzed by the most suitable procedures available. The effect of electrode site was analyzed by the non-parametric Kruskal-Wallis H test followed by specific comparisons using Ryan's procedure [11]. Because parametric tests were suitable within each electrode group, the effect of drug was analyzed separately for each electrode site by a 1-factor within-subjects analysis of variance [39].

RESULTS

Two animals in the PPC group were discarded from the experiment, one due to a faulty electrode and one due to electrode placement outside the PPC. In addition, 1 OB animal and 4 AMYG animals were discarded for failure to kindle within 21 days of stimulation. This left 11 OB, 10 PPC, and 8 AMYG animals in the study.

The performance of the 3 electrode groups during kindling is presented in Table 1. There was a significant difference among the groups in AD threshold on the first day of kindling, $H(2)=18.91$, $p<0.001$, but no significant difference in the rate of kindling, $F(2,26)=0.35$.

The effect of electrode site and drug condition on the expression of kindled seizures is summarized in Table 2 and Fig. 1. During drug testing there was a significant difference among electrode groups in AD threshold, $H(2)=20.86$, $p<0.001$, with the OB threshold significantly higher than that of the other groups (see Table 2). However, there was no significant effect of drug on AD threshold in either the OB group, $F(2,20)=0.97$, the PPC group, $F(2,18)=1.80$, or the AMYG group, $F(2,14)=0.47$.

During the determination of AD thresholds a number of animals were observed to exhibit kindling behavior (chewing movements or forelimb clonus) which occurred during the 2-sec stimulus train but which terminated with the stimulation and was not accompanied by AD's. This phenomenon occurred preferentially in the cocaine and lidocaine conditions: of the 29 animals in the experiment, 1 animal exhibited it in the saline condition, 7 in the cocaine condition, and 8 in the lidocaine condition, $\chi^2(2)=6.59$, $p<0.05$. Consequently the threshold for a behavioral response during stimulation was also analyzed. The result was similar to that for AD threshold. There was again a significant difference among the electrode groups, $H(2)=20.00$, $p<0.001$, but no significant drug effect in either the OB group, $F(2,20)=1.22$, the PPC group, $F(2,18)=0.00$, or the AMYG group, $F(2,14)=1.62$ (see Table 2).

The maximal behavioral response following stimulation at the AD threshold was rated on the 5-point scale used to score kindling. There was no significant difference among the electrode groups in behavioral response, $F(2,26)=0.94$, but there was a significant drug effect, $F(2,52)=6.51$, $p<0.01$, with a significantly stronger response occurring in the saline condition than in either the cocaine or lidocaine conditions (see Table 2). There was no significant interaction, $F(4,52)=0.27$.

The duration and maximum amplitude of the AD produced at the AD threshold were also analyzed (see Table 2). There was a significant difference in AD duration among the electrode groups, $F(2,26)=8.38$, $p<0.01$, with the AMYG group having significantly shorter AD's than the other two groups. In addition there was a significant drug effect, $F(2,52)=6.76$, $p<0.01$, with a significantly shorter AD

TABLE 2

MAIN EFFECT OF ELECTRODE SITE (OB=OLFACTORY BULB, PPC=PREPYRIFORM CORTEX, AMYG=AMYGDALA) AND DRUG (SAL=SALINE, 20C=20 mg/kg COCAINE, 20L=20 mg/kg LIDOCAINE) ON THE EXPRESSION OF KINDLED SEIZURES. DATA ARE MEANS ± SEM

	Electrode Site			Drug		
	OB	PPC	AMYG	SAL	20C	20L
Observations Per Mean	33	30	24	29	29	29
AD Threshold (μA)	218.2 ± 21.1	59.3 ± 1.72¶	57.3 ± 3.19¶	112.4 ± 21.2	118.4 ± 18.5	126.2 ± 20.9
Threshold for Behavior During Stimulation (μA)	212.1 ± 21.5	55.0 ± 1.57¶	56.3 ± 2.71¶	112.1 ± 21.1	111.2 ± 18.2	121.6 ± 21.1
Behavioral Response (Rating)	4.03 ± 0.19	4.13 ± 0.15	3.75 ± 0.20	4.45 ± 0.15	3.76 ± 0.14†	3.76 ± 0.21†
AD Duration (sec)	65.8 ± 5.24	63.3 ± 5.22	26.6 ± 7.33*#	64.6 ± 7.02	41.1 ± 4.73†	56.8 ± 7.12‡
AD Amplitude (mV)	5.76 ± 0.28	5.21 ± 0.23	2.83 ± 0.23*#	4.41 ± 0.33	4.97 ± 0.37	4.79 ± 0.38
Clonus Latency (sec)	7.09 ± 1.59	2.23 ± 0.67*	0.75 ± 0.45*	8.00 ± 1.62	1.07 ± 0.60†	1.93 ± 0.82†
Clonus Intensity (Rating)	2.61 ± 0.12	2.73 ± 0.10	1.96 ± 0.19*#	2.69 ± 0.10	2.55 ± 0.13	2.17 ± 0.17†

Specific comparisons using Ryan's procedure:
¶Significantly different from OB at 0.05 level or beyond.
Specific comparisons using Tukey's (a) test:
*Significantly different from OB at 0.05 level or beyond.
#Significantly different from PPC at 0.05 level or beyond.
†Significantly different from SAL at 0.05 level or beyond.
‡Significantly different from 20C at 0.05 level or beyond.

occurring in the cocaine condition than in either the saline or lidocaine conditions. The interaction was not significant, $F(4,52)=0.36$. There was also a significant difference among the electrode groups in maximum AD amplitude, $F(2,26)=21.63$, $p<0.001$, with the AMYG group having a significantly lower amplitude than the other two groups. There was no significant drug effect on maximum AD amplitude, $F(2,52)=1.45$, and no significant interaction, $F(4,52)=0.72$.

With regard to the significant difference in AD amplitude among the electrode groups, it should be noted that the OB and PPC are laminar structures which generate spontaneous electrical activity of high amplitude [29]; thus a high AD amplitude may be simply a reflection of a more general property of these areas. To test this possibility the AD amplitude for each animal was compared to the amplitude of pre-stimulation electrical activity (measured as the maximum peak-to-peak amplitude occurring in the 5-sec period preceding stimulation). The ratio of the maximum AD amplitude to pre-stimulation amplitude was 8.14 ± 0.61 (mean ± S.E.M.) for the OB group, 11.38 ± 0.83 for the PPC group, and 9.03 ± 1.07 for the AMYG group. The difference among the groups was significant, $F(2,26)=4.45$, $p<0.05$, with the PPC group having a significantly higher ratio than the OB group by Tukey's (a) test. The AMYG group did not differ significantly from either of the other groups by this measure.

In addition to the analyses of AD threshold data, two analyses were made pertaining to behavioral clonus. Of the 87 threshold determinations made in this experiment, there were 3 cases, all in the lidocaine condition, in which an animal did not exhibit behavioral clonus at the AD threshold. In each of these cases the AD was short (2–3 sec), and the stimulation procedure was continued until behavioral clonus was elicited during an AD. Analyses were made of the latency for clonus to occur following termination of stimulation, and the maximum intensity of the clonus as measured by the 4-point rating scale for intensity. These analyses are summarized in Table 2. For clonus latency there was a significant difference among the electrode groups, $F(2,26)=13.23$, $p<0.001$, with the latency in the OB group being significantly longer than that of the other two groups. There was also a significant drug effect, $F(2,52)=15.64$, $p<0.001$, with significantly shorter latencies occurring in both the cocaine and lidocaine conditions than in the saline condition. In addition, there was a significant interaction, $F(4,52)=7.28$, $p<0.001$. This interaction is illustrated in Fig. 1, which reveals a drug-induced decline in clonus latency in the OB and PPC groups but none in the AMYG group. However, the mean latency in the AMYG group is less than 1 sec, suggesting that the scores in this group are "bottomed out." Consequently it cannot be determined whether the drug effect is genuinely absent in the AMYG group or if it simply cannot be seen due to the near-minimum latency in the saline condition.

Finally, there was a significant difference among the electrode groups in maximum clonus intensity, $F(2,26)=8.32$, $p<0.01$, with the AMYG animals exhibiting significantly less intense clonus than the other two groups. There was also a significant drug effect, $F(2,52)=5.73$, $p<0.01$, with significantly weaker clonus occurring in the lidocaine condition than in the saline condition. The interaction was not significant, $F(4,52)=0.52$.

DISCUSSION

In comparison with the amygdala, the olfactory bulb and prepyriform cortex have received little attention in kindling studies. However, the results of this and other experiments

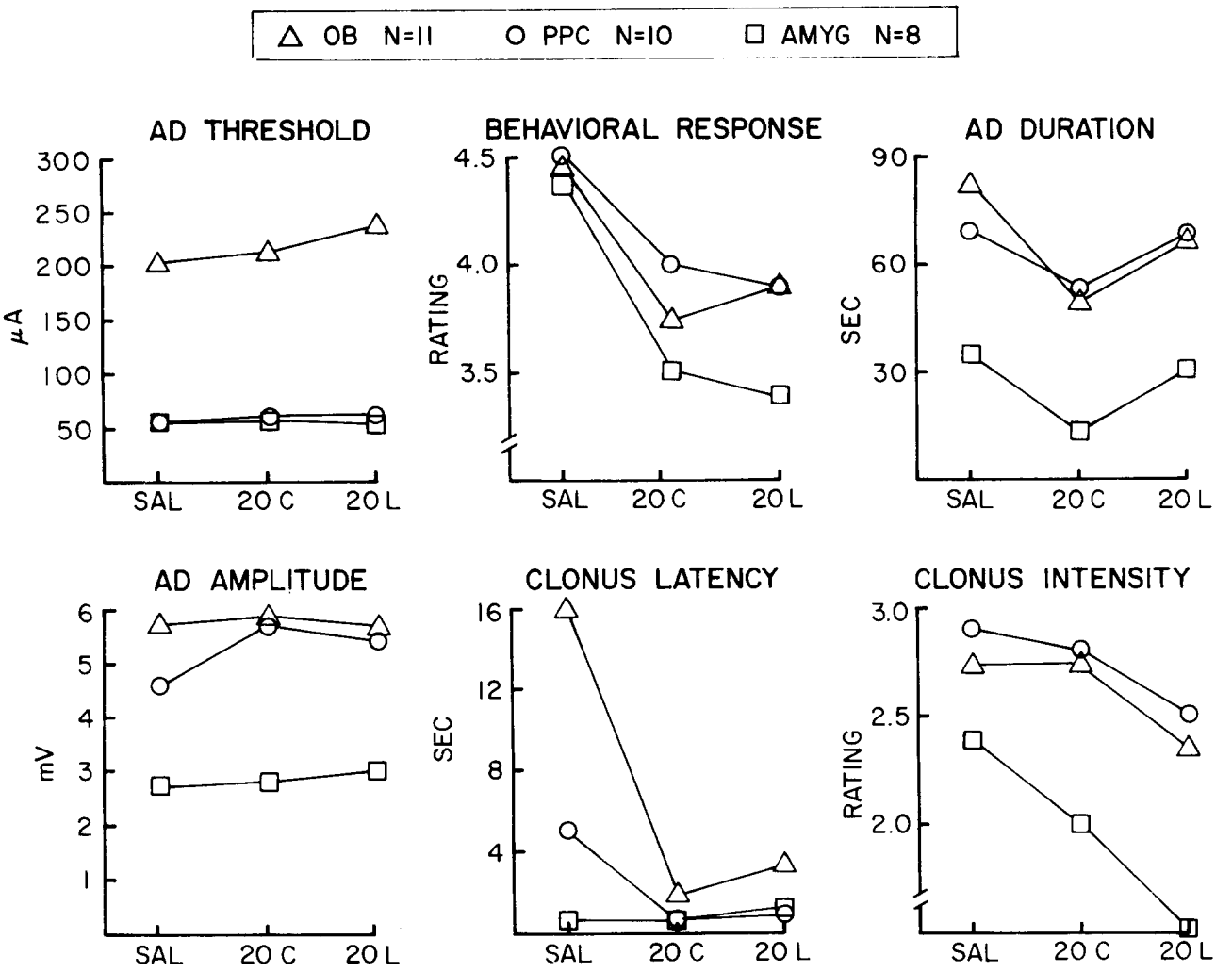

FIG. 1. The effect of electrode site (OB=olfactory bulb, PPC=prepyriform cortex, AMYG=basolateral amygdala) and drug (SAL=physiological saline, 20C=20 mg/kg cocaine hydrochloride, 20L=20 mg/kg lidocaine hydrochloride) on the expression of kindled seizures. All data points are mean values.

[2,21] suggest that kindling is at least as robust in these structures as in the amygdala. In the present experiment there was no significant difference in kindling rate among the groups when stimulated near the AD threshold for each site, and the OB and PPC groups exhibited significantly longer AD's and more intense clonus than the AMYG group. The OB and PPC groups also exhibited a significantly greater AD amplitude than the AMYG group, but this difference was eliminated when the AD amplitude was considered in proportion to the amplitude of pre-stimulation electrical activity present at the three sites.

The present experiment revealed certain drug effects common to both cocaine and lidocaine, and other effects produced by one drug but not the other. In comparison to saline both cocaine and lidocaine significantly reduced the behavioral response to stimulation and the latency for clonus to occur. Only cocaine significantly reduced the AD duration, and only lidocaine significantly reduced the intensity of clonus. With the possible exception of clonus latency, these drug effects were independent of electrode site.

The drug effect on clonus latency is perhaps the most interesting finding. Clonus latency is presumably a reflection of the propagation of seizure activity from the site of stimulation to other areas of the brain involved in the generation of the behavioral response to stimulation. Lesse and Collins [13] found that cocaine produces an increased rate of AD propagation in the cat following stimulation of either the amygdala or hippocampus. The present experiment's finding that cocaine produces a decrease in clonus latency is consistent with their result. The present experiment also found that lidocaine produces a similar decrease in clonus latency, implying that this effect is of local anesthetic origin. A positive correlation has been reported [27] between the rate of kindling in the amygdala and the speed with which clonus begins following stimulation. Consequently, reduced clonus latency may be a manifestation of the mechanism by which local anesthetics facilitate kindling [22].

Lesse and Collins also reported that cocaine produced decreased AD duration in the cat. In the present experiment this effect of cocaine was confirmed, but no significant effect of lidocaine was found. Thus the decreased AD duration produced by cocaine does not appear to be a local anesthetic

effect. This suggests that it may be due to cocaine's monoaminergic effect. The catecholamines, and particularly norepinephrine, appear to play an inhibitory role in kindling, since depletion of catecholamines or of norepinephrine alone facilitates kindling [4, 6, 16]. Callaghan and Schwark [3] reported that disulfiram, which inhibits norepinephrine synthesis, results in increased AD duration. This finding is consistent with an inhibitory role of norepinephrine in kindling and with the decrease in AD duration caused by cocaine in the present experiment. However, Wilkison and Halpern [38] reported that AD duration was decreased when catecholamine synthesis was blocked by alpha-methyl-paratyrosine, which conflicts with the preceding data on AD duration. Furthermore, selective depletion of norepinephrine can facilitate kindling without altering AD duration [4,16], which questions the relevance of AD duration to the other norepinephrine effects on kindling. Thus the functional significance of decreased AD duration and its relationship to norepinephrine are unclear at this time.

It may seem paradoxical that cocaine produces decreased clonus latency (increased AD propagation) and decreased AD duration at the same time. This may be a simultaneous manifestation of cocaine's convulsant and anticonvulsant effects. The fact that in the present experiment lidocaine also produced a decrease in clonus latency but not in AD duration suggests that these effects are due to separate pharmacological mechanisms, which would make the conflicting nature of the two effects more comprehensible.

There is an apparent conflict in the literature concerning the effect of cocaine on AD threshold. Lesse, Collins, and Denea [14] reported that cocaine lowered the AD threshold in the amygdala and hippocampus of the cat, while Matsuzaki and Misra [15] reported that cocaine elevated the threshold in the cat for AD's produced by stimulation of these same structures. The present experiment found no significant effect of either cocaine or lidocaine upon AD threshold in the olfactory bulb, prepyriform cortex, or amygdala of the rat. With regard to the present experiment, it should be noted that the AD threshold in the PPC and AMYG groups is near the lowest current level used (50 μA), making it difficult to detect any drug-induced reduction in threshold which might be present. However, there was also no significant drug effect in the OB group, in which the AD threshold was well above the minimum current level used.

There appears to be no obvious explanation for the disagreement among these three experiments on the effect of cocaine on AD threshold. While it is possible to speculate on various procedural differences among the three experiments as a possible explanation for this discrepancy, a firm resolution of this issue is dependent upon future research.

The remaining drug effects found in the present experiment merit brief comment. Lidocaine produced a decrease in rated clonus intensity, which is probably related to the mild ataxia which it produces in the dose used. Both cocaine and lidocaine produced decreased behavioral response ratings. This was primarily due to a decrease in the incidence of a stage 5 response (rearing and falling); a stage 5 response occurred 66% of the time in the saline condition (19 out of 29) but only 22% of the time in the two drug conditions (13 out of 58). This should not necessarily be interpreted as a "weakening" by the drugs of the behavioral response to stimulation. Rather it may represent a shift in the response to a form more closely resembling the clonic convulsions induced by cocaine and lidocaine, which do not include the rearing and falling seen in kindling.

In summary, the influence of cocaine on the expression of kindled seizures appears to involve some effects of local anesthetic origin and additional effects which are due to other mechanisms such as cocaine's monoaminergic action. In the present experiment these effects were observed at all of the olfactory forebrain sites studied. Other studies have reported effects of cocaine on AD threshold, propagation, and duration in the hippocampus and amygdala [13, 14, 15]. Thus the effects appear to be widespread within the limbic system and not confined to any one site.

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