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Potentiation of the Behavioral and Convulsant Effects of Cocaine by Chronic Administration in the Rat[1]

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STRIPLING, J. S. AND E. H. ELLINWOOD, JR. *Potentiation of the behavioral and convulsant effects of cocaine by chronic administration in the rat.* PHARMAC. BIOCHEM. BEHAV. 6(5) 571–579, 1977. – The effect of chronic administration on the behavioral response to cocaine was studied in male Sprague-Dawley rats. In Experiment 1 five groups of rats received daily intraperitoneal injections of either saline, 20 mg/kg, or 40 mg/kg cocaine hydrochloride for 10 days, or of higher doses of cocaine until either one or three convulsions occurred. Following this initial treatment, all animals were left untreated for seven days, and then sensitivity to cocaine was assessed in all animals by a test injection series (daily injections of increasing doses of cocaine). Animals which had received 40 mg/kg cocaine during the initial treatment exhibited a greater behavioral response (stereotyped behavior) to cocaine during the test injection series than did animals treated with saline; both the 40 mg/kg and one – convulsion treatments during the initial stage of the experiment resulted in greater sensitivity to the convulsant effect of cocaine during the test injection series. In Experiment 2 animals were injected intraperitoneally with either saline or 40 mg/kg cocaine for 10 days and then tested with a series of daily cocaine injections of increasing dosage after remaining untreated for 4, 8, 16 or 32 days. The results indicated that the initial treatment with 40 mg/kg cocaine augmented both the behavioral and convulsant effects of cocaine during the subsequent test injection series. The sensitization to the convulsant effect of cocaine was significant at all intervals after initial treatment except 16 days, while the duration of sensitization to the behavioral effects of cocaine could not be determined due to apparent age-related changes in the response of control animals to cocaine. The sensitization which was observed was attributed to the effects of cocaine per se rather than to convulsions produced by the drug.

Cocaine Chronic administration Response potentiation Stereotyped behavior Convulsions Rat

COCAINE has two major known biochemical effects: the prevention of monoamine uptake by neurons [2, 16, 30, 31, 33, 35] and a local anesthetic action [4,29]. Correspondingly, it has two classes of behavioral effects. Like amphetamine and other drugs affecting monoamine systems, it produces locomotor activity and various forms of stereotyped behavior [12, 37, 43, 46]. In high doses cocaine and other local anesthetics produce clonic convulsions [6, 32, 42, 44, 45]. Both of these behavioral effects of cocaine have been reported to undergo an augmentation with repeated administration of the drug [5, 15, 19, 27, 40]. One aspect of this phenomenon which has not yet been examined in detail is the extent to which this augmentation persists beyond the termination of chronic drug administration. The purpose of the present experiments was to study in detail the effects of chronic administration of different doses of cocaine, and the persistence of those effects.

EXPERIMENT 1

Experiment 1 was designed to determine the treatment schedule necessary to produce sensitization to cocaine, particularly to the convulsant effect of the drug. Previous studies of the convulsant effect of cocaine have demonstrated sensitization following chronic administration in one of two ways. First, repeated administration of a subconvulsive dose of cocaine can eventually result in a convulsion [5, 27, 40]. However, this effect is difficult to interpret due to the absence of a control group. For example, convulsive threshold may vary with age or body weight, both of which change during the course of chronic administration; furthermore, there is evidence that daily handling or control injections may lower the convulsive threshold [17].

A second measure of sensitization is a decrease in the number of injections between successive drug-induced

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convulsions during chronic daily administration of a high dose of cocaine [27]. Since this method does not use a control group, it also suffers from the difficulties mentioned above. In addition, it confounds the effect of chronic drug treatment per se with that of previous convulsions elicited by the drug. This is important, since convulsions induced by several commonly used convulsive agents have been found to result in a lowered convulsive threshold [1, 26, 28].

Experiment 1 was designed to examine sensitization to cocaine by a method which avoids these problems. Animals which had been chronically treated with either convulsive or subconvulsive doses of cocaine received test injections of cocaine, and their response to the drug was compared to that of animals which had been chronically treated with saline.

Method

Animals. The animals were 53 male Sprague-Dawley rats (Zivic-Miller) which weighed 220-350 g at the beginning of the experiment. They were housed individually in clear plastic cages (floor: 20 cm × 40 cm; height: 20 cm), and were maintained on a 12/12 light/dark cycle with food and water available ad libitum throughout the experiment.

Procedure. There were five groups of animals in the experiment which received three stages of treatment: an initial injection series, a waiting period, and a test injection series. During the initial injection series, the five groups were treated as follows. Two of the groups, designated as 20C and 40C, received a single daily intraperitoneal injection of either 20 or 40 mg/kg of cocaine hydrochloride for ten days. In another two groups, designated as CONV(1) and CONV(3), animals were given daily cocaine injections of increasing dosage until they had experienced either one or three clonic convulsions, respectively. The fifth group (SAL) was a saline control group. One half of the animals in this group were injected with saline for 10 days to match the 20C and 40C groups; the other half of the animals were matched to every fourth animal in the two CONV groups for the number of injections received.

The initial injection series for the two CONV groups was as follows: Days 1-7, 55 mg/kg; Days 8-12, 60 mg/kg; Days 13-15, 65 mg/kg. This schedule was designed to produce a gradually increasing convulsant effect, utilizing the effects of repeated administration as well as increasing dosage.

In the rat, a cocaine-induced clonic convulsion consists of a primary episode of continual clonic jerks which may or may not be followed by one or more secondary episodes separated by periods without clonic activity. For the purpose of the experiment a convulsion was defined as a clonic episode with a total duration of 20 sec or longer, and was characterized by three measures: (A) the duration in seconds of the primary seizure; (B) the total duration in seconds of the seizure from onset to the last secondary seizure; and (C) the number of 15 sec periods between the onset and termination of the seizure during which clonic seizure activity was present. This last measure was intended to reflect the total amount of seizure activity. The total duration does not necessarily serve this purpose, since in some animals short secondary episodes may occur several minutes apart.

Throughout the experiment animals were observed carefully for 30 min following injection for the occurrence of a convulsion. During the initial injection series, diazepam (1 mg/kg IP) was administered to stop a convulsion if secondary activity continued for three minutes beyond the onset of the primary seizure. This was done to minimize fatalities and to avoid the aphagia which may follow severe convulsions. All animals which experienced a convulsion were given wet mash in their cages until any weight loss was regained. In addition, animals in the CONV(3) group were not given additional injections of cocaine until any weight loss following the convulsion was regained.

Following the initial injection series there was a waiting period of 7 days, during which the animals were not injected. This period was inserted between the initial and test injection series to allow transitory effects of the initial injection series to wear off.

The test injection series began for each animal on the eighth day after its last injection in the initial injection series. All animals were treated identically in this stage of the experiment. The following ascending-dose series was used: 1 day at 45 mg/kg; 1 day at 50 mg/kg; 7 days at 55 mg/kg; 5 days at 60 mg/kg; and 3 days at 65 mg/kg. The test injection series was terminated for each animal after one convulsion had been produced. The purpose of this injection series was to assess the sensitivity of the various groups to the convulsant effect of cocaine. The variable used to measure this sensitivity was the number of injections in the series required to produce a convulsion. It was anticipated that this schedule would provide a very sensitive measure, since the repeated administration of each of the higher doses would allow sensitization to develop to that dose before proceeding to the next dose. During the test injection series, diazepam was not given unless a convulsion persisted for 10 min rather than 3 min, in order to obtain more information on seizure duration.

On the first day of the test injection series, each animal was rated by an experienced observer for its behavioral response to 45 mg/kg cocaine using a modification of a rating scale developed in our laboratory for the purpose of assessing the behavioral effects of stimulant drugs [8]. Behavior was rated over a 10 sec period once per minute for 15 min following injection. Behavior was rated on the scale from 1 to 8 as follows: (1) asleep (lying down, eyes closed); (2) inactive (lying or sitting, eyes open); (3) in-place activity (grooming); (4) normal, alert, active (moving about cage, sniffing, rearing); (5) hyperactive (rapid running movements); (6) slow patterned (stereotyped locomotor activity, usually circling the cage perimeter); (7) fast patterned (fast stereotyped locomotor activity); (8) restricted (stereotyped head and/or forelimb movements without locomotor activity).

All testing of animals was done in their home cages between the fifth and eighth hours of the light period. Solutions of cocaine hydrochloride were prepared in physiological saline with the concentration adjusted so that animals received 1 ml/kg body weight.

Analysis. Eight animals died from convulsions during the initial injection series. This left the following number of subjects in each group: SAL – 10; 20C – 10; 40C – 9; CONV(1) – 8; CONV(3) – 8. Although one animal in the CONV(3) group failed to develop a convulsion during the 15-day initial injection series, it was retained in the experiment to avoid selective discard of animals from one group.

Due to individual differences in the convulsive threshold to cocaine, four of the five groups contained an animal which did not convulse during the 17 day test injection

series. This posed a problem for the analysis of the number of injections required to produce a convulsion during the test injection series. To solve this problem without introducing a bias, the animal with the largest number of injections in each group was not included in this analysis.

When parametric tests were appropriate, data were analyzed by analyses of variance followed by individual comparisons using the Newman-Keuls method [47]. Nonparametric statistics were used for variables which were not normally distributed, and for the number of injections required to produce a convulsion during the test injection series, since the dose increases in the test injection series were not evenly spaced. In these cases, the data were analyzed by the Kruskal-Wallace H test or the Friedman analysis of variance by ranks for repeated measures, with the Mann-Whitney U test used for individual comparisons [36].

Results

Initial injection series. During the initial injection series animals treated with cocaine gained weight more slowly than saline animals. In addition, individual animals lost significant amounts of weight following convulsions. However, the wet mash placed in these animals' cages compensated for the weight loss. The rate of weight gain for the groups from the first day of the experiment to the first day of the test injection series, expressed as a percentage of the weight gained in the saline group, was as follows: 20C (100.1%); 40C (98.7%); CONV(1) (95.6%); CONV(3) (94.7%). While this difference is significant, $F(4,39) = 2.77$, $p<0.05$, the differences are quite small and indicate that even in the two CONV groups the animal body weights had recovered to near normal levels at the beginning of the test injection series. Thus it is difficult to attribute differences in seizure susceptibility during the test injection series to physical debilitation.

During the initial injection series, the CONV(1) group received an average of 5.63 injections of cocaine, while the CONV(3) group received an average of 10.25 injections of cocaine. Thus the duration of treatment for the CONV(3) group was comparable to that received by the 20C and 40C groups while the CONV(1) group received treatment of shorter duration.

The seizure parameters for the CONV(3) group during the initial injection series are shown in Fig. 1. As can be seen there was a trend for all parameters to increase from the first to the third convulsion. This trend was significant

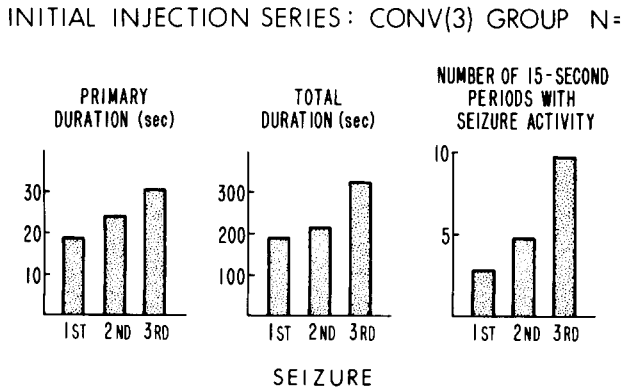

FIG. 1. Experiment 1. Mean scizure parameters for the CONV (3) group during the initial injection series.

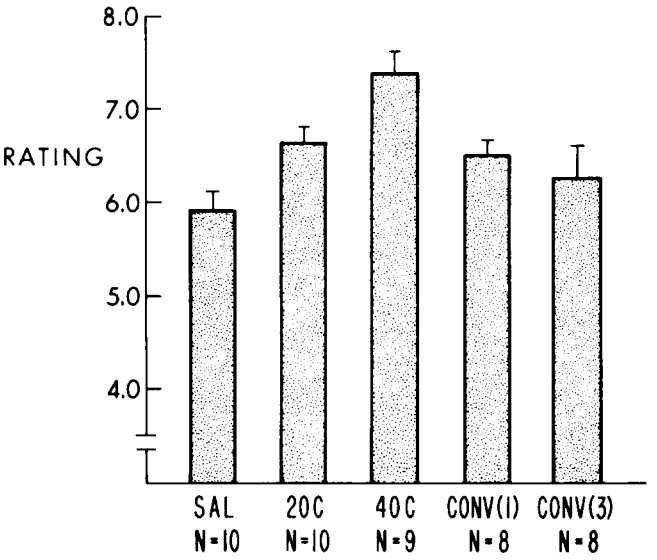

FIG. 2. Experiment 1. Mean behavioral rating and S.E.M. for the five groups over the 15 min period following injection of 45 mg/kg cocaine on the first day of the test injection series.

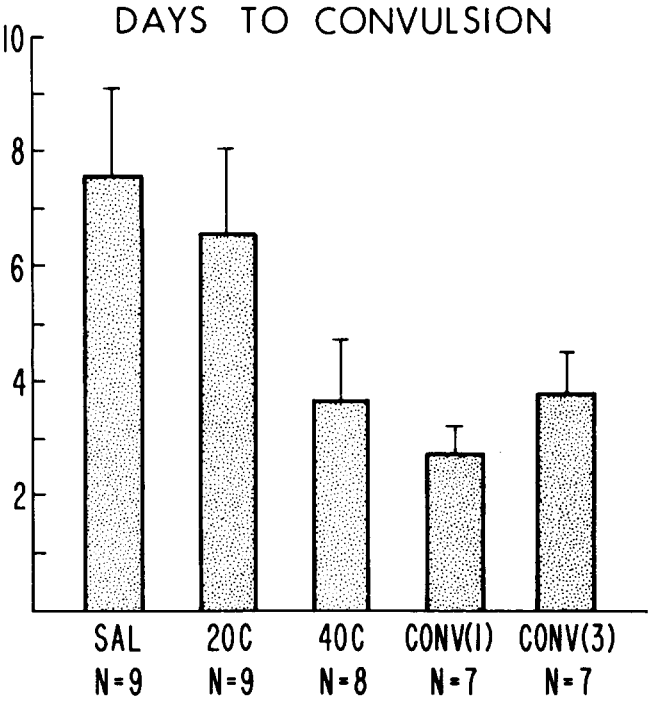

FIG. 3. Experiment 1. Mean days-to-convulsion and S.E.M. for the five groups during the test injection series.

only for primary duration, $F(2,12) = 4.03$, $p<0.05$, and the number of 15 sec periods containing seizure activity (Friedman analysis of variance by ranks; $\chi_r^2 = 7.9$; $df = 1$, $p<0.02$). Thus the amount of seizure activity present during a convulsion increased as a function of the number of previous convulsions.

Test injection series. The behavioral response to the injection of 45 mg/kg cocaine on the first day of the test injection series is shown in Fig. 2. A single-factor analysis of variance indicated a highly significant difference among the groups, $F(4,40) = 5.92$, $p<0.01$. Individual comparisons by the Newman-Keuls procedure indicated that the 40C group

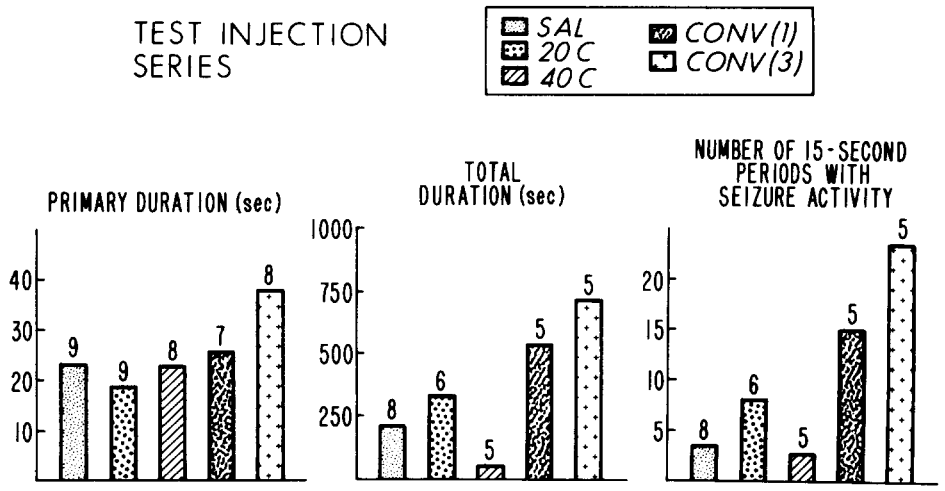

FIG. 4. Experiment 1. Mean seizure parameters for the five groups during the test injection period. The number of animals per group is shown above each bar.

had a significantly greater response to cocaine than did the SAL ($q = 6.33$, $p<0.05$), the 20C ($q = 2.91$, $p<0.05$), the CONV(1) ($q = 3.85$, $p<0.05$), or the CONV(3) ($q = 4.92$, $p<0.05$) groups. No other comparisons were significant.

The number of days required for a seizure to occur during the test injection series is shown in Fig. 3. A Kruskal-Wallace H test indicated that there was a significant difference among the groups ($H = 11.95$, $df = 4$, $p<0.02$). The nature of this difference was analyzed by comparison of each cocaine group with the SAL group using the Mann-Whitney U test. Both the 40C group ($U = 12.5$, $p<0.05$, two-tailed) and CONV(1) group ($U = 7.0$, $p<0.02$, two-tailed) convulsed significantly sooner than the SAL group. In addition, the CONV(3) group approached significance ($U = 12.5$, $p<0.10$, two-tailed). While the 40C group was intended to represent a high but subconvulsive level of treatment, three of the animals in that group convulsed during the initial injection series, and consequently the increased sensitivity to cocaine in this group cannot be attributed to a purely subconvulsive initial treatment.

The seizure parameters for the five groups during the test injection series are shown in Fig. 4. During the test injection series 12 animals out of the 45 in the experiment died during convulsions. Because the total duration and number of 15 sec periods of seizure activity were cut short in the animals that died, analysis of these measures included only animals which survived the convulsions. Primary duration was analyzed by analysis of variance, while the other measures were analyzed by the Kruskal-Wallace H test. The groups differed significantly in both total duration ($H = 14.57$, $p<0.01$) and the number of 15 sec segments of seizure activity ($H = 17.22$, $p<0.01$), but not in primary duration. $F(4,36) = 2.31$, $p<0.10$. Mann-Whitney U tests indicated that only the two CONV groups had a significantly greater total duration and number of 15 sec periods of seizure activity than did the SAL group (CONV(1): $U = 5$, $p<0.015$ and $U = 0$, $p<0.001$; CONV(3): $U = 0$, $p<0.001$ and $U = 0$, $p<0.001$; all p values two-tailed).

EXPERIMENT 2

Experiment 1 indicated that chronic administration of a convulsive dose of cocaine produces a sensitization to the drug's convulsant effect. However, the question of whether chronic administration of a sub-convulsive dose can also produce sensitization was left unanswered, since three animals in the 40C group convulsed during initial treatment. Experiment 2 was designed to address this point and also to assess the extent to which the sensitization to cocaine persists beyond the termination of chronic administration.

Method

Animals. The animals were 66 male Sprague-Dawley rats (Zivic-Miller) which weighed 240–320 g at the beginning of the experiment. Their housing conditions were identical to those of Experiment 1.

Procedure. Like Experiment 1 this experiment had three parts: an initial injection series, a waiting period, and a test injection series. There were five groups: a saline group (SAL) and four cocaine groups. During the initial injection series, all animals were injected intraperitoneally once per day for 10 days. The SAL group received saline and all the cocaine groups received 40 mg/kg cocaine. Two animals died from convulsions during the initial injection series, leaving 64 animals in the study: 16 in the SAL group and 12 in each of the cocaine groups. Following the initial injection series, the four cocaine groups, designated as 40C-4, 40C-8, 40C-16, and 40C-32, were left untreated for a waiting period of 4, 8, 16, or 32 days, respectively. The SAL group was divided into four subgroups ($N = 4$ each) which were matched to the four cocaine groups for duration of the waiting period. Following the waiting period all animals underwent an identical test injection series which began at 45 mg/kg cocaine and increased each day by 2.5 mg/kg. Injections were terminated for each animal when that animal had a clonic convulsion of a total duration of 20 sec or longer, or if it reached 77.5 mg/kg without convulsing. Because the dose of cocaine in the test injection series increased in regular daily increments, parametric statistics were used to analyze the dose at which the animals convulsed.

During the first 48 hr of the initial injection series daily food consumption of the groups was measured to de-

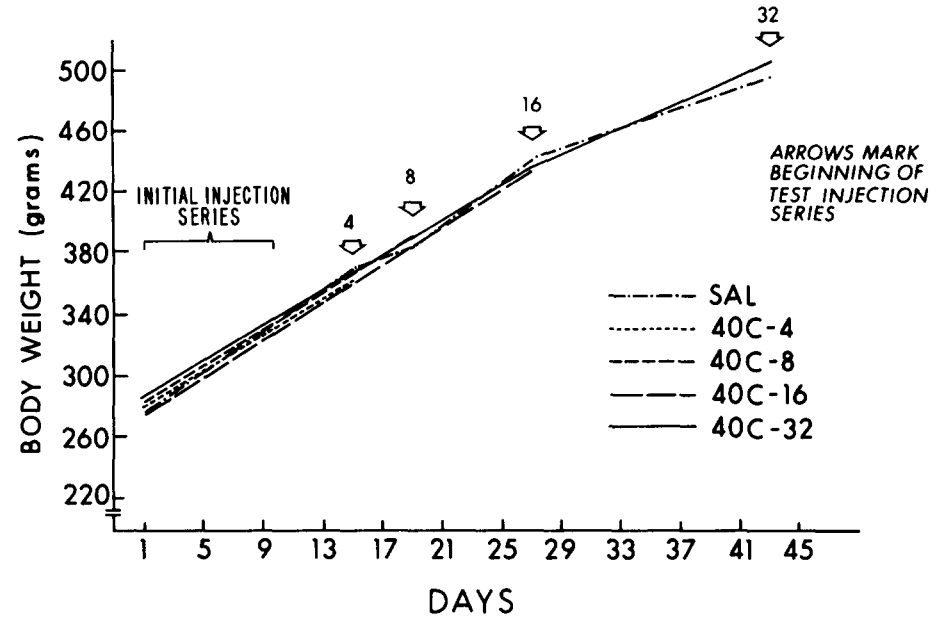

FIG. 5. Experiment 2. Mean body weight for the five groups from the beginning of the initial injection series to the beginning of the test injection series. Each point in the SAL curve represents only those SAL animals which are not yet beyond the beginning of the test injection series.

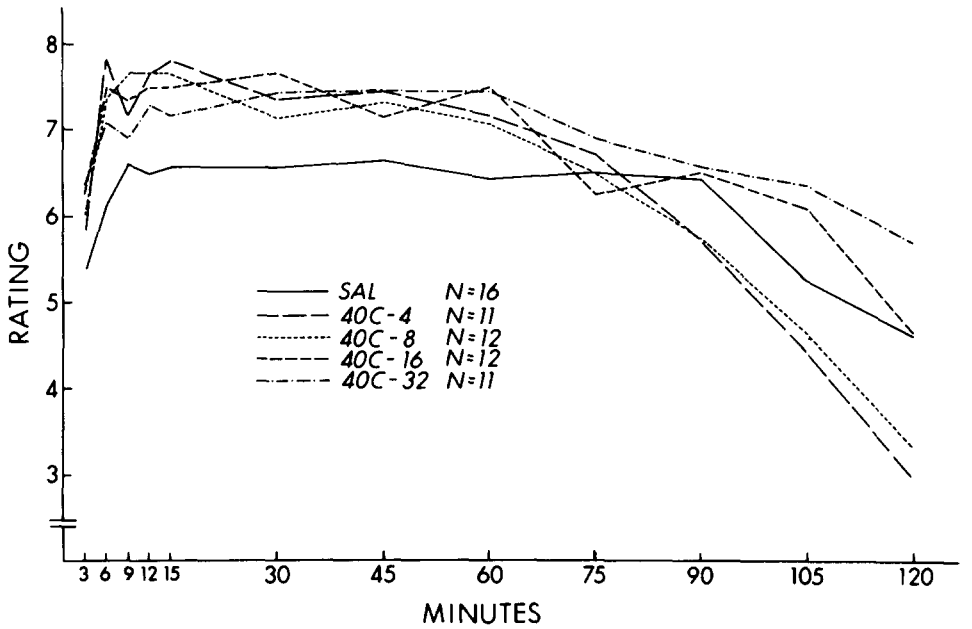

FIG. 6. Experiment 2. Mean behavioral rating for the five groups over the 120 min period following injection of 45 mg/kg cocaine on the first day of the test injection series.

termine the magnitude of cocaine's effect on food intake. Subsequent to this point, animals in the cocaine groups received food pellets in their cages to counteract the cocaine-induced reduction in weight increase, while SAL animals were placed on a slightly restricted feeding schedule (90% of the ad lib amount). These manipulations remained in effect until the sixth day of the waiting period, except for the SAL-4 and 40C-4 animals, which were returned to normal feeding on the third day of the waiting period (48 hr before the beginning of their test injection series).

On the first day of the test injection series the behavioral response to 45 mg/kg cocaine was rated for all animals. The behavior for each animal was rated over a 10 sec period every 3 min for the first 15 min postinjection, and every 15 min thereafter until 120 min postinjection. The rating scale was the same as that used in Experiment 1.

All data were collected between the fifth and eighth hours of the light period. Drug solutions were prepared as in Experiment 1. All animals were closely observed for 30 min following injection, and convulsions were scored as in Experiment 1. The data were analyzed by the procedures used in Experiment 1 and by Dunnett's t-test [47].

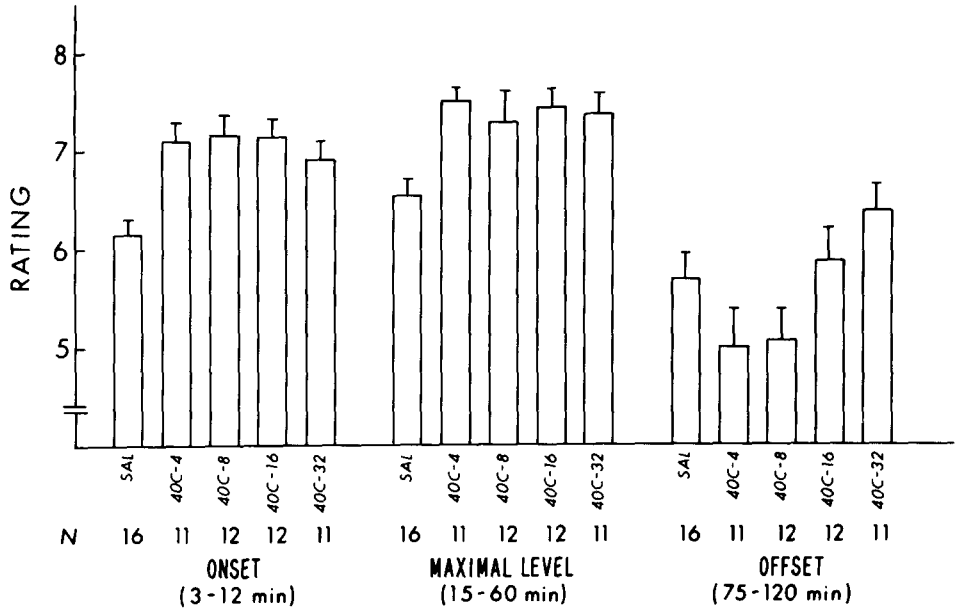

FIG. 7. Experiment 2. Mean behavioral rating and S.E.M. for the five groups over three blocks of time following injection of 45 mg/kg cocaine on the first day of the test injection series.

Results

The animals in the cocaine groups had a significantly lower food consumption than did SAL controls over the first 48 hr of the initial injection series (26.1 vs 29.1 g; $F(1,62) = 10.64$, $p<0.01$). However, Fig. 5 illustrates that the feeding manipulations employed resulted in comparable body weights in the SAL and cocaine groups throughout the course of the experiment.

The behavioral response to 45 mg/kg cocaine on the first day of the test injection series is shown in Fig. 6. Two animals were not included in this figure and the subsequent analysis: one in the 40C-32 group which was the only animal to convulse on the first day of the test injection series, and one in the 40C-4 group which did not exhibit a behavioral response to the injection, having a mean rating of 2.38 over the first hour vs 5.50 as the next lowest score in the experiment. For the purpose of analysis the data were pooled into three blocks intended to reflect the onset (Min 3-12), maximal level (Min 15-60), and offset (Min 75-120) of the drug effect (Fig. 7). A single-factor analysis of variance indicated that there was a significant difference among the groups in each of the three blocks (onset: $F(4,57) = 5.75$, $p<0.01$; maximal level: $F(4,57) = 3.59$, $p<0.05$; offset: $F(4,57) = 3.18$, $p<0.05$). Individual comparisons with the SAL group via Dunnett's t-test indicated that all of the cocaine groups had a significantly greater behavioral response than the SAL group during onset (40C-4: $t = 3.47$, $p<0.01$; 40C-8; $t = 3.87$, $p<0.01$; 40C-16: $t = 3.79$, $p<0.01$; 40C-32: $t = 2.81$, $p<0.05$; all p values two-tailed) and all but the 40C-8 group had a significantly greater maximal level (40C-4: $t = 3.10$, $p<0.05$; 40C-8: $t = 2.48$, $p<0.10$; 40C-16: $t = 2.97$, $p<0.05$; 40C-32: $t = 2.66$, $p<0.05$; all p values two-tailed). However, no cocaine group was significantly different from the SAL group during offset. Examination of Figs. 6 and 7 indicates that the significant overall differeng among the groups during offset reflects a more rapid offset of the drug effect in animals tested after the shorter waiting periods.

Figure 8 shows a breakdown of the response to cocaine among the SAL animals. There was no significant difference among the four subgroups during the onset, $F(3,12) = 0.60$, or maximal level, $F(3,12) = 1.39$, $p>0.25$, of the drug effect, but there was a significant difference during the offset, $F(3,12) = 3.62$, $p<0.05$. As with the cocaine groups, the SAL subgroups tested earliest had a more rapid offset of the drug effect.

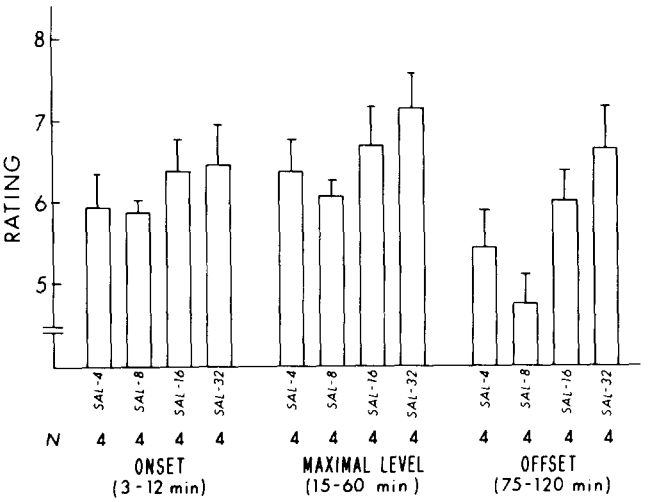

FIG. 8. Experiment 2. Mean behavioral rating and S.E.M. for the four SAL subgroups over three blocks of time following injection of 45 mg/kg cocaine on the first day of the test injection series.

Seizure susceptibility was measured by the dose at which a convulsion occurred during the test injection series. Several of the groups contained an animal which did not convulse during the test injection series, and to solve this problem without bias the highest score in each group was discarded from the analysis. Under these conditions (Fig. 9A), there was a highly significant difference among the groups, $F(4,54) = 4.80$, $p<0.01$. Individual comparisons with the SAL group by means of Dunnett's t-test indicated that the

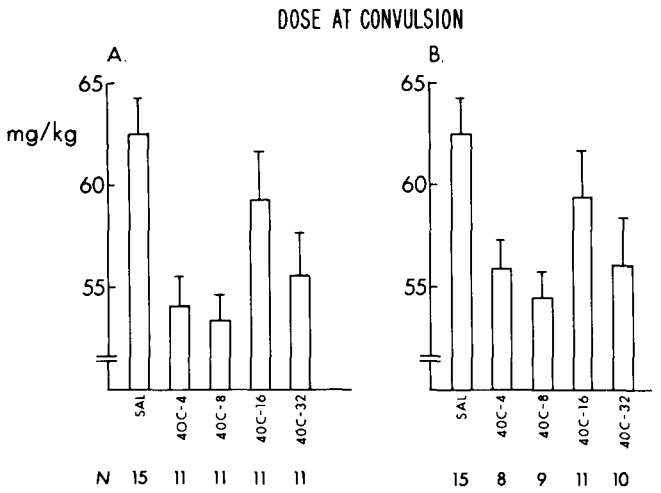

FIG. 9. Experiment 2. Mean dose at convulsion and S.E.M. for the five groups during the test injection series. (A) Highest score/group discarded; (B) Highest score/group and scores of all animals which convulsed during the initial injection series discarded.

40C-4 (t = 3.37, $p<0.01$), 40C-8 (t = 3.64, $p<0.01$), and 40C-32 (t = 2.73, $p<0.05$) groups, but not the 40C-16 group (t = 1.28), were significantly more sensitive to the convulsant effect of cocaine than the SAL group (all p values two-tailed). However, this effect cannot be attributed to a purely subconvulsive level of treatment, because six of the animals in the cocaine groups convulsed during the initial injection series. If these animals are discarded, so that only animals which received a purely subconvulsive level of cocaine treatment during the initial injection series are analyzed (Fig. 9B), there is still a significant overall difference among the groups, $F(4,48) = 3.12$, $p<0.05$. Using a two-tailed test only the 40C-8 group has a significantly lower convulsive dose (t = 3.00, $p<0.05$), while the 40C-4 (t 2.35, $p<0.10$) and 40C-32 (t = 2.50, $p<0.10$) groups approach significance. However, given the directional nature of the hypothesis being tested (that chronic cocaine administration lowers the convulsive threshold to cocaine), one-tailed tests are appropriate, in which case the 40C-4 and 40C-32 groups are significantly more sensitive to cocaine than the SAL group at the 0.05 level, and the 40C-8 group at the 0.025 level.

There was no significant difference among the SAL subgroups in sensitivity to the convulsant effect of cocaine (Fig. 10; $F(3,12) = 0.43$). None of the seizure parameters (initial duration, total duration, or number of 15 sec periods of seizure activity) varied significantly as a function of the drug administered during the initial injection period or the duration of the waiting period.

DISCUSSION

The results of the present experiments confirm previous reports that the chronic administration of cocaine can result in augmentation of its behavioral effects. Furthermore, this augmentation was found to persist beyond the termination of chronic drug administration. Experiment 1 indicated a persistence for at least 8 days of both the enhanced stereotyped behavior and the enhanced convulsant effect of cocaine, but Experiment 2 did not pinpoint the duration of this enhancement. The stereotyped behavior produced by cocaine in Experiment 2 was significantly greater in all cocaine groups than in the SAL

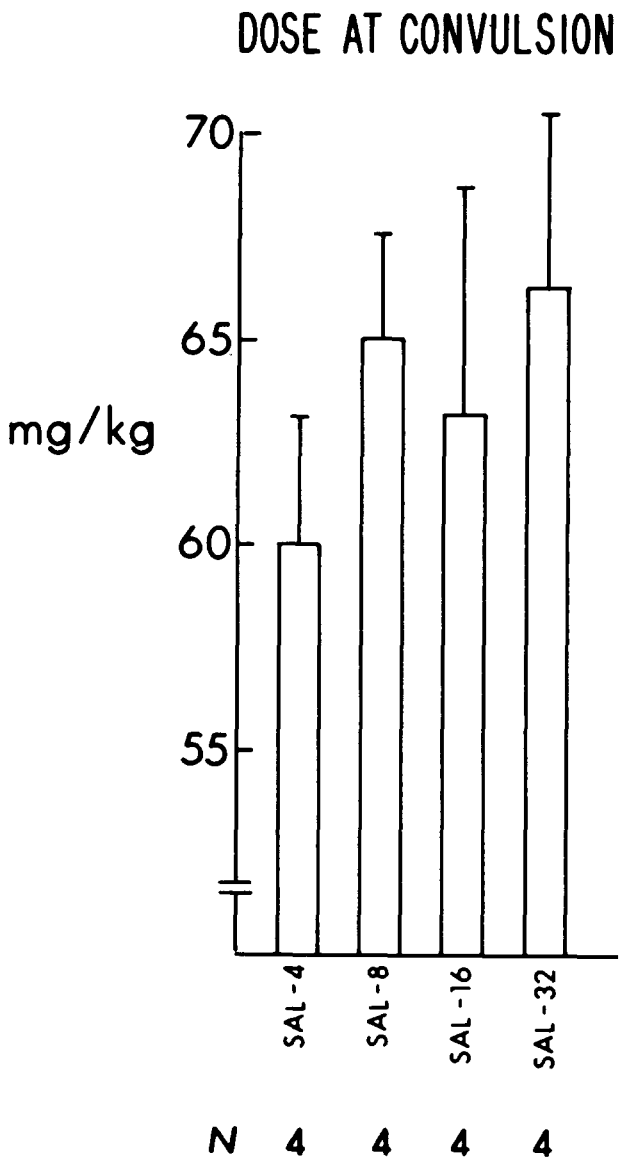

FIG. 10. Experiment 2. Mean dose at convulsion and S.E.M. for the four SAL subgroups during the test injection series.

group for the first hr postinjection, but trends among the SAL subgroups (see Fig. 8), although not significant, suggest that the significant enhancement of stereotypy in the cocaine groups with the longest waiting periods (40C-16 and 40C-32) may have been due at least in part to an increase in response with age. The significant difference among both the 40C groups and the SAL subgroups during the second hour postinjection indicates that the rate of offset of the cocaine effect decreases with age (see Figs. 6, 7, and 8). Other work in our laboratory has indicated that naive rats have similar age-related differences in offset when injected with cocaine for the first time [20]. This change could be a secondary effect of the body weight increase associated with increasing age in the rat (Fig. 5), or related to other changes with age such as reduced degradative metabolism of drugs [18].

The period of time during which the convulsant effect of cocaine remained enhanced in Experiment 2 is also un-

certain. It can be argued that the effect persisted for 33 days or more after termination of drug administration, since the 40C-32 group exhibited a significant enhancement, while the SAL subgroups showed no tendency for sensitivity to increase with duration of the waiting period. However, the absence of a significant persistence in the 40C-16 group weakens this interpretation. The significant effects in the 40C-4 and 40C-8 groups indicate that the sensitization persisted for at least 9 days after the end of initial treatment, but the conflicting results in the 40C-16 and 40C-32 groups do not clearly establish the duration of this persistence.

Several points can be made about the nature of the enhanced response to cocaine. Administration of either 40 mg/kg cocaine or the CONV(1) treatment produced an increased convulsant effect of cocaine in Experiment 1. Experiment 2 demonstrated that a purely subconvulsive level of cocaine treatment (40 mg/kg) could result in a reduced convulsive threshold to cocaine. In Experiment 1 the 40 mg/kg treatment but not the CONV treatments resulted in augmentation of stereotyped behavior. Thus the enhancement of both these effects of cocaine seems due primarily to the effects of the drug per se rather than the convulsions produced by the drug. In contrast, Experiment 1 showed that only the CONV treatments increased the amount of seizure activity present during a convulsion, and in Experiment 2 the chronic administration of 40 mg/kg cocaine had no effect on this measure. These findings demonstrate a distinction between the convulsive threshold to cocaine and the intensity of the resulting convulsion, with the latter being affected only when convulsions were produced during the initial treatment. This difference may be a reflection of different mechanisms underlying these two aspects of convulsions [13].

We have recently demonstrated that the chronic administration of cocaine results in a persistent augmentation of the drug's electrophysiological as well as behavioral effects [39]. The mechanisms by which chronic cocaine produces these effects are not known. The results of the present experiments indicate that the augmented behavioral response is not related to any debilitation produced in the animals by chronic cocaine administration. Although Experiment 2 demonstrated a small reduction in food consumption due to cocaine, the animals receiving chronic cocaine treatment continued to gain weight, and the enhanced response they showed was in comparison to saline-treated animals matched for weight gain. This finding suggests that the enhanced response to cocaine is a fairly specific effect of chronic administration rather than being related to the general physiological condition of the animal.

A number of possible explanations for this enhanced response can be formulated, including (a) the development of a conditioned response to the drug; (b) an increase in the amount of drug reaching its sites of action due to accumulation in the brain or alterations in absorption, entry into the brain, or degradation; or (c) an increased responsiveness of the brain to the drug due to changes in receptor sensitivity or the repetition of the electrophysiological effects of cocaine in a manner resembling the kindling phenomenon of Goddard [14]. These possibilities and the evidence bearing on them have been discussed in detail elsewhere [9, 38, 39].

In addition to cocaine, d-amphetamine has also been reported to produce an augmented response (locomotor activity and stereotyped behavior) following chronic administration [19, 21, 25, 34]. This sensitization to certain behavioral effects of these two psychomotor stimulants contrasts with the tolerance which occurs to the hyperthermic, anorectic, and lethal effects of the drugs [11, 22, 23, 41]. If sensitization such as that reported here also occurs in humans, it may be related to the development of pathological behavior which has been observed in humans during chronic use of high doses of these drugs [3, 7, 10, 24]; consequently, experimental analysis of the mechanisms underlying the sensitization in animals may provide information relevant to the behavior changes which occur in human users of these drugs.

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