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Cocaine-Induced Oscillation Is Conditionable

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KUCINSKI, B. J., S. M. ANTELMAN, A. R. CAGGIULA, H. FOWLER, S. GERSHON, AND D. J. EDWARDS. *Cocaine-induced oscillation is conditionable.* PHARMACOL BIOCHEM BEHAV **63**(3) 449–455, 1999.—We have recently shown that under some circumstances, sensitization produced by a stimulant such as cocaine (COC) can give way, with successive drug administrations, to alternating attenuations and reinstatements of the effect, an outcome that we have termed oscillation. Because sensitization to COC can be conditioned, we inquired whether COC-induced oscillation also was conditionable. The end point used was shock-induced hypoalgesia (paw withdrawal from a hot plate), as we have previously shown that oscillation follows initial sensitization of this measure with one to five pretreatments of 12 mg/kg (IP) of COC spaced at 1-week intervals, with the last COC injection occurring 30 min prior to the footshock. Experiment 1 indicated that a conditioned stimulus (CS)—a distinctive environment—which repeatedly had been paired with COC, would substitute for the last COC injection in sustaining the oscillatory effect. Experiment 2 showed that a previously established CS successfully substituted for all COC injections in first inducing sensitization that was then followed by oscillation. These findings strongly suggest that COC-induced oscillation shares with COC-induced sensitization, the property that both can be conditioned.

Cocaine-induced oscillation Sensitization Conditioning Stress-induced hypoalgesia

MODERN biological theories of drug addiction emphasize the central importance of Pavlovian conditioning in maintaining the addictive behavior and promoting its relapse [e.g., (6,7,11,13,16)]. According to this view, neuroadaptive processes at the core of addiction, such as tolerance and sensitization, become at least in part dependent for their expression on the presence of environmental stimuli that have been previously associated with the drug. For example, when a drug like morphine or cocaine (COC) is administered repeatedly to rats in a distinctive environment, the future expression of a sensitized response to that drug is dependent on administering the drug in the same environment (14,18). The conditionability of a putative adaptive process is thus one of the hallmarks of its potential as an important factor in addiction.

We have recently proposed a homeostatic model of drug sensitization that states that as sensitization to repeated drug exposure grows, the action of opposing, homeostatic processes results in an oscillatory pattern of responsiveness to subsequent drug exposures, with the oscillation typically occurring around the initial drug response (1,3,5). Support for this model comes from a large series of experiments involving neurochemical, endocrine, or behavioral end points, which demonstrate that oscillation, either by itself or preceded by sensitization, can be evoked by successive combinations of drug treatments (2,4,12). For all cases, intermittent weekly treatments led to an alternating pattern of increases and decreases (oscillation) in the response to each subsequent treatment.

In an attempt to investigate further the relationship between sensitization and oscillation, we asked whether oscillation shared with sensitization the property of being susceptible to Pavlovian conditioning. We had previously shown that in rats given one to five COC injections at weekly intervals, sensitization of the hypoalgesic response to footshock occurred after one COC injection and reached its maximum after two injections; but thereafter oscillation developed such that the sensitization effect was attenuated by three compared to two COC injections, reinstated by four injections, and then reattenuated after five COC treatments [see Fig. 2 in (5); closed bars "a" through "f" of Fig. 2 herein closely approximate the previously observed oscillatory effects, with the ex-

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ception that bar "e" should be as high as bar "c"). In the present two experiments we asked whether this same pattern—sensitization followed by oscillation—was conditionable. In the first study, a conditioned stimulus (CS)—a distinctive environment—that had been paired repeatedly with COC, the unconditioned stimulus (US), was found to substitute for the last COC injection in sustaining the oscillatory pattern. In the second experiment, a previously established CS successfully substituted for all five COC injections in first inducing sensitization, which was then followed by oscillation.

METHOD

Subjects

For both experiments, experimentally naive male Sprague–Dawley rats, 125–150 g in weight, were purchased from the Zivic-Miller Co. (Allison Park, PA). Upon arrival, the rats were caged individually in a colony room where a 12-h, reversed day/night cycle was effected through artificial illumination. All rats were maintained on ad lib food and water throughout each experiment. After a 2-day travel-recovery period following their arrival, the animals were handled and weighed daily for 5 days. Thereafter, the experimental manipulations began, with the animals being weighed on alternate days. All daily experimental manipulations started at 2 h into the dark phase of the day/night cycle, which extended from 0700–1900 h.

Apparatus

Shock administration. Two identical rodent chambers (Coulbourn Instruments, Lehigh Valley, PA, Model E10-10), measuring 25 × 30 × 33 cm, served as the shock apparatus. Each chamber had clear Plexiglas side walls, sheet-metal top and end walls, and a grid floor consisting of bars, 0.24 cm in diameter, spaced 0.87 cm apart. The grid floor of each chamber was connected through timer circuitry to the output of a shock generator and scrambler (BRS/LVE, Beltsville, MD, Models 903 and SC902) to provide an aversive US: a 5-s, 2-mA footshock. The chambers were individually housed in identical sound-attenuating cubicles, 50 × 60 × 88 cm, that were located in a room adjacent to the programming equipment. A 100-W, 120-V bulb, recessed behind a frosted glass plate in the ceiling of each cubicle, was operated at 85 V, AC, to provide diffuse illumination of the chamber. An ambient sound level of 72 dB was provided by operating the cubicle's ventilating fan at 57 V, AC. Hereafter, this room containing the shock apparatus will be referred to as the chamber room.

Hypoalgesia test. A portable thermal-sensitivity ("hot-plate") test apparatus, positioned on a movable cart 2 feet from each shock chamber, was used to assess shock-induced hypoalgesia. The hot plate consisted of a 30-cm square copper plate, fitted with a clear Plexiglas cyclinder, 26 cm (interior diameter) × 36 cm. The copper plate and its water-tight cylinder were immersed to a depth of 3 cm in a thermostatically controlled water bath (Fisher Scientific, Pittsburgh, PA, Circular Model 73) that maintained the plate's surface temperature at 52°C. A Standard Electric timer (Standard Electric Time Co., Springfield, MA), adjacent to the hot plate, was used to measure the rat's latency to lick its hind paw or to jump from the plate. Immediately thereafter, the rat was removed from the hot plate.

Drug administration. Cocaine hydrochloride (COC) was injected intraperitoneally (IP) at a dose of 12 mg/kg. Unless otherwise noted, all injections were spaced 1 week apart, with the last occurring 30 min prior to shock and the analgesia test in the chamber room.

Conditioning environments. Two rooms, both different from the chamber room, were used to assess conditioning effects stemming from the injections of COC in a particular environment. One was the colony room (COL), where the animals were housed continuously and attended to only during the dark phase of their day/night cycle; the other was a distinctively different experimental room (DIST) to which selected groups were transported for their COC injections. The DIST room had the following distinctive features by comparison with the COL room, which was twice as large: a series of full-sized filing cabinets against one wall and a single, one-sided rack of cages against the other, as opposed to multiple, double-sided cages completely filling the COL room; sound attenuation afforded by a carpeted floor and acoustical tiles on the ceiling and walls, as opposed to a concrete floor and impervious wash-down walls in the COL room; bright, overhead fluorescent lighting and a pine fragrance provided by an air freshener, as opposed to dim, indirect incandescent lighting (during the dark phase) and a "sterile" odor provided by the daily use of an antisceptic cleaner in the COL room; and a small centrally located table with only injection paraphernalia on it, as opposed to a large bench-top table with a scale, recording material, and injection paraphernalia, located along one side of the COL room. In addition, the injection routines were different in the two rooms: in the COL room, each animal was removed from its home cage for weighing and/or injection and was then returned to its home cage; in the DIST room, to which each animal was transported in its home cage, covered with a lid, the animal was placed in a holding cage (similar to its home cage) while the experimenter prepared the COC injection, was then removed from the holding cage for injection, returned to the holding cage for 30 min, and then returned to its home cage and transported back to the COL room.

Procedure

To habituate the rats of each experiment to the analgesia test apparatus, they were given two separate exposures, spaced 1 week apart, to that apparatus 5–6 weeks prior to their scheduled test. This involved transporting each rat in its home cage to the chamber room and then placing the animal in the test apparatus for 2 min, with the water bath set at room temperature. Thereafter, the animal was returned to the colony room.

Experiment 1. For this experiment, 100 rats were randomly assigned to 10 groups of 10 animals each. However, one animal from each of two groups died during the course of the experiment, reducing the *n* to 98.

To duplicate COC's oscillatory sensitization effect on shock-induced hypoalgesia, as well as to assess the role of conditioning on that effect, different pairs of control groups were given four or five weekly COC injections in the COL and/or DIST room prior to shock and the analgesia test. The selected number of COC pretreatments (four or five) was based on two considerations: 1) the fact that our prior studies (3,5) had consistently shown that, relative to a shock-only control, two and four COC pretreatments produced a marked increase in hot-plate latencies, whereas three and five COC pretreatments appreciably reduced that effect; and 2) the fact that a sufficient number of COC pretreatments had to be administered to generate a conditioning effect. Consequently, if COC's oscillatory sensitization effect were to be modulated by conditioning, that modulation would be evident with more

(four and five) rather than fewer (two and three) COC pretreatments.

The first pair of groups received their four or five COC injections, including that on the test day, in the COL room. Hence, these two groups are designated COL/COL, CS/COC to indicate that their COC treatments, both prior to and on the test day, occurred in the COL room, and that the COL room was present as a CS for COC on the test day. On that day, 30 min after their last COC injection in the COL room, the rats of these two groups were transported to the chamber room where they were placed in the shock chamber for 10 s, shocked, and, immediately afterward, removed from the chamber and placed on the hot plate for the analgesia test. This pair of groups was treated identically to those used in our prior studies and, therefore, served as standard, comparison groups (see Table 1 for a summary of the procedure for these two groups, as well as for the other groups in Experiment 1).

To assess the effect of a conditioning environment other than the COL room on COC's oscillatory sensitization effect, a second pair of groups was given all of their four or five COC injections in the DIST room. Thus, these two groups are designated DIST/DIST, CS/COC to indicate that their COC injections, both prior to and on the test day, occurred in the DIST room, and that the DIST room was present as a CS for COC on the test day. On that day, following their customary COC injection and 30-min detention in the DIST room, the rats of these two groups were transported directly to the chamber room, placed in the shock chamber for 10 s, shocked, and, immediately afterward, removed from the chamber and placed on the hot plate for the analgesia test.

To assess the effect of COC in the absence of the COL-room CS, a third pair of groups was given four or five COC injections, exactly like the first pair of groups, except that on the test day, they were transported to the DIST room (i.e., a novel room), injected and then detained in that room for 30 min, exactly like the second pair of groups. Thus, this pair of groups is designated COL/DIST, COC-alone to indicate their respective treatments prior to and on the test day, and the absence of their COL-room CS on the test day. On that day, following their injection and 30-min detention in the DIST room, they were transported directly to the chamber room, shocked, and tested for hypoalgesia exactly like the other groups.

To assess the effect of an environmental CS by itself, a fourth pair of groups was given three or four COC injections in the DIST room on all treatment days preceding the test day, exactly like the second pair of groups; however, on the test day, this fourth pair of groups was transported to and detained for 30 min in the DIST room but was not given any COC injection on that day. Thus, these two groups are designated DIST/DIST, CS-alone to indicate that they were exposed to only their DIST-room CS on the test day. Following their 30-min detention in the DIST room on the test day, they were transported directly to the chamber room, shocked, and tested for hypoalgesia exactly like the other groups.

Because the CS-alone pair of groups did not match the other pairs of groups in the number of COC injections received (three and four vs. four and five), another CS-alone group was added and treated exactly like the three and four COC, CS-alone groups, except that it received five weekly COC injections prior to its exposure to only the DIST-room CS on the test day. Accordingly, if the DIST-room CS simulated the effect of COC for the CS-alone groups, the three and four COC CS-alone groups would show enhanced and attenuated latencies, respectively, like the four and five COC groups, whereas the five COC CS-alone group would show a reenhanced latency, in evidence of the CS's control of the oscillatory sensitization effect.

To control for the effects of COC and/or its environmental CS, a 10th group was not given any COC injections prior to the hypoalgesia test. Instead, the animals of this group were left undisturbed in their home cages (except for routine weighing) until the test day. On that day, they were transported directly to the chamber room, where they were shocked and tested for hypoalgesia exactly like the other groups. Thus, this group is designated a shock-only group.

Experiment 2. For this experiment, 90 rats were randomly assigned to nine groups of 10 rats each. Seven of these groups were initially given a total of 16 consecutive pairings of the DIST-room CS and the COC US, administered once per day between the hours of 0900 and 1200 h. On each conditioning day, the rats were transported to the DIST room, where they received an IP injection of COC, and then were detained in holding cages (similar to their home cages) for 30 min while COC exerted its effect. After their 30-min CS exposure, the rats were returned to the COL room where they remained undisturbed until the next conditioning day. The transportation and injection routines were the same as those described earlier.

Following the initial conditioning phase, all animals were

TABLE 1
GROUP TREATMENTS FOR EXPERIMENT 1

Group			Conditioning Trials	Test Day Procedure
1	COL/COL	CS/COC	3 pairings of COL & COC	COL & COC / shock / test
2	COL/COL	CS/COC	4 pairings of COL & COC	COL & COC / shock / test
3	DIST/DIST	CS/COC	3 pairings of DIST & COC	DIST & COC / shock / test
4	DIST/DIST	CS/COC	4 pairings of DIST & COC	DIST & COC / shock / test
5	COL/DIST	COC ALONE	3 pairings of COL & COC	DIST & COC / shock / test
6	COL/DIST	COC ALONE	4 pairings of COL & COC	DIST & COC / shock / test
7	DIST/DIST	CS ALONE	3 pairings of DIST & COC	DIST —/ shock / test
8	DIST/DIST	CS ALONE	4 pairings of DIST & COC	DIST —/ shock / test
9	DIST/DIST	CS ALONE	5 pairings of DIST & COC	DIST —/ shock / test
10	Shock only		None	— —/ shock / test

COC = Cocaine Administration; COL = Colony Room; DIST = Distinctive Experimental Room.

given a 2-week rest period, during which they remained undisturbed in their home cages, except for weighing on alternate days. The purpose of the rest period was to allow the animals' physiologic systems to recover and any residual effects of COC to dissipate. During this rest period, all rats were given two habituation exposures, spaced 1 week apart, to the hypoalgesia test apparatus. As before, this involved transporting the rats to the chamber room and placing them in the test apparatus for 2 min, with the water bath set at room temperature.

For the second phase of the experiment, five of the conditioned groups were exposed to the DIST-room CS by itself, without any COC injections. These five groups were given a total of one, two, three, four, or five CS-alone exposures, on a weekly basis, with the last occurring on the test day, 30 min prior to test. For each weekly CS exposure, the rats were transported to the DIST room and placed in the holding cages for 30 min. After all but their last CS exposure on the test day, the animals were returned to the COL room where they remained undisturbed (except for routine weighing) until the following week. Immediately after their exposure to the DIST-room CS on the test day, the animals were transported directly to the chamber room, where they were shocked and tested for hypoalgesia, as previously described (see Table 2 for a summary of the procedure for these five groups, as well as for the other groups of Experiment 2).

The sixth and seventh groups served as shock-only controls. One of these groups had received the initial 16 days of conditioning but was not exposed to the CS during the second experimental phase. The other was not given any conditioning during the initial phase, or exposure to the CS during the second phase. During the second phase, both groups remained undisturbed in their home cages until the test day. On that day, both groups were transported directly to the chamber room, shocked, and tested for hypoalgesia, as earlier described.

The eighth and ninth groups served as no-treatment controls. The procedures for these two groups were identical to those for the shock-only controls, with the exception that they were not shocked on the test day. Thus, on the test day, these two groups were transported to the chamber room and placed immediately on the hot plate for the hypoalgesia test.

Data Analysis

For each experiment, individual latencies from the analgesia test were subjected to a one-way analysis of variance. Significant overall group effects were then partitioned by preplanned orthogonal polynomial contrasts [based on our earlier findings, e.g., (5)] to assess expected differences among the groups and/or major trend effects. Where appropriate, ancillary contrasts were employed to confirm or clarify established effects. [For a detailed description of this statistical technique, see (9).]

RESULTS

Experiment 1

Figure 1 presents the mean hot-plate latencies for the 10 groups of Experiment 1. As shown, relative to the shock-only control, the standard pretreatments of four and five COC injections in the colony room, both prior to and on the test day (COL/COL), produced, respectively, a pronounced sensitization effect (i.e., longer latencies on the hot plate) and a virtually complete attenuation of that effect, in affirmation of its oscillatory nature. Figure 1 shows that those results were duplicated, respectively, by the four and five COC pretreatment groups, which received all of their injections in the distinctive experimental room (DIST/DIST), even though the mean latencies for these groups were shorter than those for their COL/COL counterparts. That duplication indicates that the oscillatory sensitizing effects of cocaine are not offset by transporting animals to a distinctive room for their COC injections. Figure 1 also shows that the same effects occurred, respectively, for the four and five COC groups that received their injections in the colony room prior to and then in the distinctive experimental (i.e., a novel) room on the test day (COL/DIST). That outcome indicates that the absence of the colony-room CS on the test day, i.e., COC alone, did not diminish the oscillatory effects. However, the most fascinating

TABLE 2
GROUP TREATMENTS FOR EXPERIMENT 2

	GROUP	CONDITIONING TRIALS	REST PERIOD	CS EXPOSURE	TEST DAY PROCEDURE
1	1 CS	1 daily pairing - DIST & COC for 16 days	2 Wks	NONE	CS / shock / test
2	2 CS	1 daily pairing - DIST & COC for 16 days	2 Wks	1CS; 1 week prior to test	CS / shock / test
3	3 CS	1 daily pairing - DIST & COC for 16 days	2 Wks	2 CS; 1 and 2 weeks prior to test	CS / shock / test
4	4 CS	1 daily pairing - DIST & COC for 16 days	2 Wks	3 CS; 1, 2 and 3 weeks prior to test	CS / shock / test
5	5 CS	1 daily pairing - DIST & COC for 16 days	2 Wks	4 CS; 1, 2, 3 and 4 weeks prior to test	CS / shock / test
6	Shock only	NONE	2 Wks	NONE	-- / shock / test
7	Shock only	1 daily pairing - DIST & COC for 16 days	2 Wks	NONE	-- / shock / test
8	No treatment	NONE	2 Wks	NONE	-- / ----- / test
9	No treatment	1 daily pairing - DIST & COC for 16 days	2 Wks	NONE	-- / ----- / test

COC = Cocaine Administration; DIST = Distinctive Experimental Room.

result shown in Fig. 1 is that the same respective effects also occurred for the three and four COC groups that received all of their injections in the distinctive room (DIST/DIST), but only the CS on the test day. That outcome attests to a conditioning effect because it indicates that the CS itself functionally served as a US, in place of the COC injection. Moreover, in line with that conditioning effect, the five COC CS-alone group showed a reinstatement of the sensitization effect that was observed, not only for the three COC CS-alone group, but also for the four COC-alone group and the four CS/COC groups, in further evidence of the CS's modulation of the oscillatory effect.

In support of the above description, the results of an analysis of variance of the latency data showed a highly reliable overall group effect, $F(9, 88) = 8.53, p < 0.001$. Partitioning of this overall group effect by preplanned orthogonal contrasts indicated that, for groups exposed to the distinctive room on the test day, there was no reliable difference between the four CS/COC and the four COC-alone groups, nor between the three and five COC CS-alone groups, nor between those two sets. However, those four groups showed a marginally reliable difference from the four CS/COC group treated in the colony room on the test day, $F(1, 88) = 3.53, p = 0.064$, in evidence of a slightly reduced sensitization effect for rats treated in the distinctive room on the test day. Similarly, for groups exposed to the distinctive room on the test day, there was no reliable difference between the five CS/COC and the five COC-alone groups, nor between those two groups and the four COC CS-alone group. However, those three groups were reliably different from the five CS/COC group that was treated in the colony room on the test day, $F(1, 88) = 7.43, p = 0.008$, again in evidence of a somewhat reduced effect of treatment in the distinctive room on the test day. In addition, those four groups were not reliably different from the shock-only group but, collectively, those five groups differed reliably from the other five groups that exhibited a sensitization effect, $F(1, 88) = 59.94, p < 0.001$. In confirmation of these effects, ancillary contrasts showed that there was a reliable difference between the sensitized and nonsensitized groups of each pair, Fs$(1, 88) > 8.48$, ps < 0.006, and that all of the sensitized groups were reliably different from the shock only group, $F(1, 88) = 10.22, p < 0.002$.

To further confirm the above results, ancillary contrasts were also performed to assess factorial (i.e., row, column, and interaction) effects for matched pairs of groups; specifically, the four vs. five CS/COC (both COL/COL and DIST/DIST), the four vs. five COC-alone, and the three vs. four COC CS-alone groups. Like the above results, this factorial analysis showed a highly reliable difference between the four sensitized and the four nonsensitized groups, $F(1, 88) = 56.28, p < 0.001$, and a reliable difference between the groups treated in either the colony room or the distinctive experimental room on the test day, $F(1, 88) = 9.94, p = 0.002$. However, there were no reliable interaction effects for these or any other comparisons, and no other significant group effects.

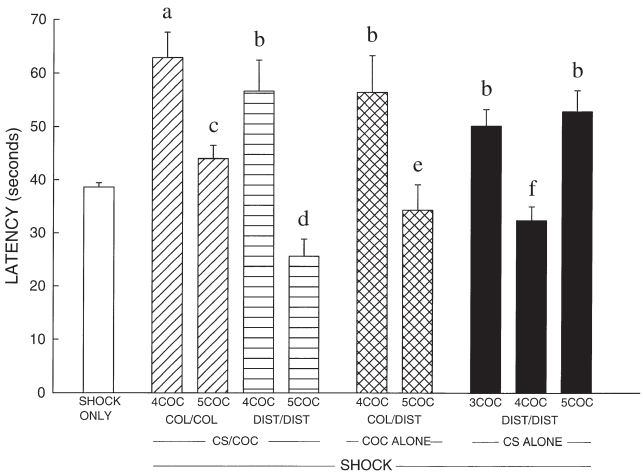

FIG. 1. Cocaine (COC) conditioning Experiment I: shock-induced hypoalgesia following three to five pairings of either colony (COL) room or distinct (DIST) room cues (CS) with a 12 mg/kg, IP. COC US (n = 10/group), specifically chosen to assess oscillation. All CS/US pretreatments were spaced 1 week apart, with the last treatment 30 min prior to shock and test. Open bars = shock only. Side and horizontal hatched bars = groups that received four or five pairings of either the COL or DIST room CS and COC US. Crosshatched bars = groups that received either three or four COL room/COC pairings, but on the test day received COC in the DIST room (novel CS). Solid bars = groups that received three to five DIST room/COC pairings, but on the test day were exposed to the CS-alone (no COC). $^{a}p < 0.001$ vs. shock only; all $^{b}p < 0.001$ vs. shock only; $^{c}p = 0.002$ vs. four COC COL/COL CS/COC; $^{d}p < 0.001$ vs. four COC DIST/DIST CS/COC; $^{e}p < 0.001$ vs. four COC COL/DIST CS-alone; $^{f}p < 0.006$ vs. three or five COC DIST/DIST CS-alone. See text for further details of the statistical results.

Experiment 2

Figure 2 presents the mean hot-plate latencies for the nine groups of Experiment 2. As shown, relative to the two no-treatment groups, which did not differ, all of the groups receiving shock, either alone or in conjunction with an immediately preceding CS exposure on the test day, exhibited markedly increased latencies on the hot plate, in evidence of a shock-induced hypoalgesic effect. In addition, relative to the two shock-only groups, which did not differ, the five CS groups collectively showed longer latencies on the hot plate, in evidence of a CS-induced sensitization effect. Furthermore, exactly like the findings of our prior studies assessing the effects of successive COC treatments on shock-induced hypoalgesia (3,5), Fig. 2 shows that the CS groups exhibited an oscillatory sensitization effect that increased up to two CS treatments prior to test, then decreased, increased, and decreased again with three, four, and five CS treatments prior to test. [Note, also, the similarity of results for the four and five CS groups of this study with those for the three and four COC (then) CS-alone groups of Experiment 1, shown in Fig. 1.]

In support of the above description, the results of an analysis of variance of the latency data showed that there was a highly reliable overall group effect, $F(8, 81) = 31.91, p < 0.001$. Partitioning of this overall effect by preplanned orthogonal contrasts indicated that there was no difference between the conditioned and nonconditioned no-treatment groups, nor between the conditioned and nonconditioned shock-only groups. However, the two shock-only groups differed reliably from the five CS groups, $F(1, 81) = 80.92, p < 0.001$, and, collectively (as well as individually), the two shock-only and the five CS groups differed reliably from the two no-treatment groups, $F(1, 81) = 189.32, p < 0.001$. In addition, trend analysis by orthogonal contrasts of the data for the five CS groups indicated that there was both a highly reliable quartic (up-down-up-down) effect, $F(1, 81) = 30.97, p < 0.001$, and a reliable decreasing linear effect, $F(1, 81) = 16.03, p < 0.001$, across the groups receiving one through five CS treatments

prior to test. Those trend effects represent the best description of the data for the five CS groups because they accounted for virtually all (93.7%) of the variance among those groups, and thus all residual trend variance was nonsignificant. In further confirmation of this CS-induced oscillatory sensitization effect and its slight attenuation over successive CS treatments, ancillary contrasts showed that the difference between any two adjacent CS groups was reliable, Fs(1, 81) > 5.31, ps < 0.025, and that the two and three CS groups had reliably longer latencies than the four and five CS groups, $F(1, 81) = 8.7$, $p < 0.005$.

DISCUSSION

The results of both experiments provide strong evidence that the oscillatory sensitization effects of COC on shock-induced hypoalgesia can be mediated by a distinctive-room CS that has been explicitly paired with COC as a US. Experiment 1 showed that, after three and four COC injections in a distinctive experimental room, exposure to that room alone on the test day generated the same sensitized and nonsensitized (i.e., heightened and lowered) latencies on the hot plate as occurred, respectively, for groups that had received a total of four and five COC injections prior to test, administered either all in the colony room or all in the distinctive room, or in the colony room with the last occurring in the distinctive room (without the colony room CS) on the test day. Furthermore, a group given five injections of COC in the distinctive room showed a reinstatement of the sensitization effect when exposed to only the distinctive-room CS on the test day. Thus, for the three, four, and five COC CS-alone groups of Experiment 1, the distinctive-room CS functioned exactly as if COC had been administered on the test day.

Experiment 2 showed similar results in that after 16 daily injections of COC in the distinctive experimental room, successive weekly presentations of that distinctive-room CS by itself produced exactly the same oscillatory sensitization (up-down-up-down) effects as had been observed in our prior research with repeated weekly injections of COC (3,5). Indeed, the only difference between the results of Experiment 2 and our earlier findings on COC is that the present CS-induced sensitization effects were somewhat attenuated for the four and five CS groups. However, that outcome is perfectly amenable to a conditioning interpretation because repeated presentations of a CS by itself will progressively extinguish and thus weaken its conditioned effect.

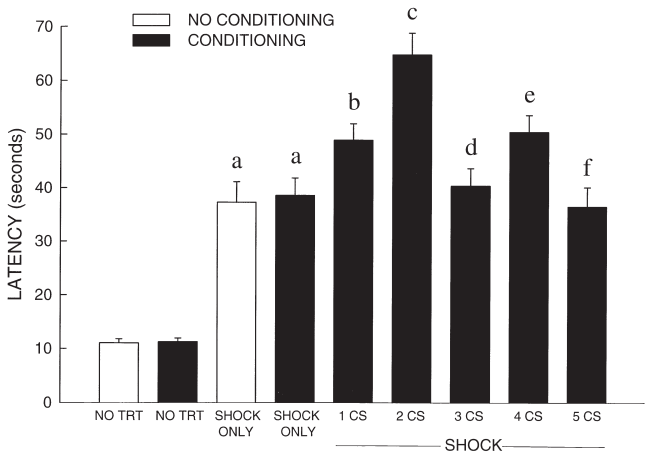

FIG. 2. Cocaine (COC) conditioning Experiment II: shock-induced hypoalgesia after one to five CS-alone exposures with the distinctive room cues (CS) that had previously been paired with a COC (12 mg/kg, IP) US. All CS-alone exposures were spaced 1 week apart with the last treatment 30 min prior to shock and test. Open bars = groups that had no prior CS/US pairings. Solid bars = groups that had prior CS/US pairings. [a]$p < 0.001$ vs. NO TRT; [b]$p = 0.021$ vs. prior conditioning shock only; [c]$p < 0.001$ vs. one CS-alone; [d]$p < 0.001$ vs. two CS-alone; $p = 0.024$ vs. three CS-alone; [f]$p = 0.002$ vs. four CS-alone. See text for further details of the statistical results.

The results of the present experiments are also in line with the findings of other studies showing a conditioned sensitization effect [for a review, see (18)]. Those studies have demonstrated that environmental stimuli that are explicitly paired with an opiate or stimulant drug, for example, morphine, cocaine, amphetamine, not only will facilitate that drug's sensitizing effect on some behavioral end point (by contrast with neutral and explicitly unpaired stimuli), but will also engender a cross-sensitization effect when presented in conjunction with a different type drug. More relevant to the present findings, such paired stimuli will also strongly mimic the effect of their associated drug when presented in the absence of that (or another) drug; and, true to their conditioned nature, they will extinguish their conditioned sensitization effect when repeatedly presented alone. It is equally noteworthy that explicitly unpaired stimuli can also acquire a conditioned effect: that of predicting the absence of the drug and thus of counteracting or inhibiting the drug's sensitization effect when presented in conjunction with that drug. As robust as these conditioned sensitization phenomena are, they are nonetheless limited by the fact that, to date, their influence has been demonstrated only for the initial sensitizing effect that a drug can exert on some behavioral end point, and not for the oscillatory sensitization effects that are produced by intermittent presentations of the drug on a weekly (as opposed to daily) basis. Thus, the present findings reinforce and extend the generality of the role of conditioning in sensitization phenomena by showing that an explicitly paired context will also mimic the drug's oscillatory sensitization effects when presented on the same intermittent schedule as the drug, but in the absence of that drug.

Because conditioning is thought to play a central role in addiction (6,7,13), and we have shown that oscillation can be conditioned, we may ask whether this conditioned oscillation is relevant to the addiction process. Oscillation, by definition, is a phenomenon in which the end points being studied—whether behavioral or neurochemical—wax and wane; in other words, the highs and lows of each cycle, and are, therefore, intermittent. It has long been known that while rapid tolerance tends to develop to continuous or closely spaced drug exposure, sustained effects are much more likely after intermittent exposure. Thus, by imposing a forced intermittency on the organism after repeated COC experiences, the oscillation phenomenon may act to strengthen the reinforcing efficacy and addictive potential of drugs (8,10,15,17). Moreover, the waxing and waning in the ability of a conditioned stimulus to evoke a COC-like effect might lead to the prediction that the effectiveness of drug-related stimuli in eliciting craving and promoting relapse would also fluctuate upon repeated encounters.

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